PKB INHIBITORS AS ANTI-TUMOR AGENTS

Field of the Invention

The present invention encompasses compounds and compositions thereof useful as kinases inhibitors, in particular serine/threonine kinases such as PKB. The invention also encompasses methods of treating cancer and/or restenosis inhibition.

Background of the Invention

Serine/threonine kinase PKB, also known as Akt, has a critical regulatory role in numerous cellular events. The human genome contains three PKB isoforms (PKBα, PKBβ and PKBγ) that are highly homologous on the protein level. Jones *et al.*, "Molecular cloning and identification of a novel serine/threonine protein kinase (PKB)." *Proc. Natl. Acad. Sci.* USA88, 4171-4175 (1991). The α and β isoforms are expressed ubiquitously while the expression of PKBγ appears to be more restricted. Konishi, *et al.* "Molecular cloning and characterization of a new member of the RAC protein kinase family, association of the pleckstrin homology domain of three types of RAC protein kinase with protein kinase C subspecies and beta gamma subunits of G proteins," *Biochem. Biophys. Res. Commun.* 216, 526-534 (1995). The specific biological roles of the PKB isoforms remain to be delineated. Two homologues of the viral oncogene were identified in the human genome and were called Akt1and Akt2 corresponding to PKBα and PKBβ. All PKB isoforms have the same general structure consisting of an N-terminal pleckstrin-homology (PH) domain, a catalytic domain and a C-terminal regulatory domain.

PKB mediates PI3K activation in, among others, the following categories: (a) mediating cell survival by modulating the activity of apoptotic signals; (b) regulation of cell growth; and (c) modulation of glucose homeostasis.

Many forms of cellular stress induce apoptosis including DNA damage, irradiation, hypoxia, loss of attachment to the extracellular matrix, radiation and the withdrawal of growth factors. These pro-apoptotic stimuli are counterbalanced by the action of PKB which regulates cell survival either directly through the inhibition of a component of the cell-death machinery or indirectly through transcriptional mechanisms. The principal pro-apoptotic protein regulated by PKB is the BCL-2 family member BAD. Datta, *et al.*, "Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery," *Cell*, 91, 841-847 (1997).

PKB positively regulates the transcription factor NF-κB whose activity is central to cell proliferation and survival. This regulation by PKB is mediated by the phosphorylation and activation of NF-κB regulator kinases that in turn phosphorylate the inhibitory cofactor I-κB. Subsequent degradation of I-κB permits the translocation of NF-κB to the nucleus and transcription of several survival genes. Kane, *et. al.*, "Induction of NF-kB by the Akt/PKB kinase," *Curr. Biol.* 9, 601-604 (1999).

PKB influences the cell cycle by inactivating two cyclin-dependent kinase inhibitors, $p27^{Kip}$ and p21 Cip1/Waf. Mothe-Satney, *et al.*, "Multiple mechanisms control phosphorylation of PHAS-I in five (S/T)P sites that govern translational repression," *Mol. Cell. Biol.* 20, 3558-3567 (2000). Upon phosphorylation by PKB, $p27^{Kip}$ is relocalized from the nucleus to the cytoplasm where it cannot inhibit the cyclin-dependent kinase CDK2 leading to cell-cycle progression. Similarly, phosphorylation of p21 Cip1/Waf by PKB lead to cytoplasmic localization of this inhibitory protein and consequent cell proliferation. Zhou BP, *et al.*, "Cytoplasmic localization of p21Cip1/WAF1 by Akt-induced phosphorylation in HER-2/neu-overexpressing cells," *Nat. Cell Biol.*, 3(3), 245-252 (2001).

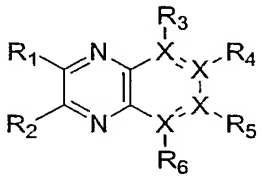
PKB has been recognized as an important target for the treatment of cancer. Czech, *et al.*, "Signaling mechanisms that regulate glucose transport," *J. Biol. Chem. 274*, 1865-1868 (1999). PKB signaling can influence tumorigenesis through direct or indirect mechanisms. One direct mechanism is based on the constitutive activation of PKB in tumors due to PH-domain independent localization of PKB at the plasma membrane that reduces the requirement for PI3-kinase in PKB activation. Di Cristofano, *et al.*, "The multiple roles of PTEN in tumor suppression," Cell, *100*, 387-390 (2000). This mechanism is the basis for the oncogenic activity of v-Akt. The product of this gene is a chimera of viral gag protein and PKB. The PKB kinase in the chimaera is constitutively active because the N-terminal myristic acid targets the protein to the plasma membrane in the absence of the PH domain. *Id.* Another direct tumorigenic mechanism of PKB is based on the over-expression of specific PKB isoforms in transformed cells. For example, PKBb has been found to be amplified in human pancreatic adenocarcinoma and ovarian carcinomas, while upregulation of PKBg has been associated with carcinomas of the breast and prostate. Cheng, *et al.*, "AKT2, a putative oncogene encoding a member of a subfamily of protein-serine/threonine kinases, is amplified in human ovarian carcinomas," *Proc. Natl. Acad. Sci. U.S.A.*, 89, 9267-9271 (1992). Indirect effects of

PKB on tumorigenesis many are associated with mutation of the PTEN tumor suppressor gene. PTEN is a phosphatidylinositol phosphatese that is an upstream negative regulator of PKB that is critical in the termination of PI3K-mediated signaling. Nakatani, *et al.*, "Up-regulation of Akt3 in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer lines," *J. Biol. Chem. 274*, 21528-21532 (1999). PTEN tumor suppressor gene is mutated in hereditary cancers of the breast and thyroid and in several other tumor types. Stambolic, *et al.*, "Negative regulation of PKB/Akt-dependent cell survival by the tumour suppressor PTEN," *Cell*, 95, 29-39 (1998). Tumors associated with loss of PTEN activity have elevated levels of phosphorylated PKB and consequently increased growth rates and reduced activity of apoptotic pathways.

Accordingly, there is a need for novel PKB inhibitors that are readily available, easy to synthesize, and/or effective in low dosages.

Summary of the Invention

One embodiment of the invention encompasses compounds of Formula (I):



Formula I

wherein,

X is N or C;

R_1 and R_2 each independently is:

1) hydrogen;
2) alkyl;
3) alkoxy;
4) cycloalkyl;
5) heterocyclyl;
6) heterocyclylalkyl;
7) aryl;
8) heteroaryl;
9) aralkyl;
10) heteroaralkyl; or
11) $-NH_2$, $-NHR_8$, or $-NR_8R_8$;

wherein both R_1 and R_2 are not hydrogen, R_8 is independently hydroxyl, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, and optionally, R_1 and R_2 may be taken together to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_3, R_4, R_5, and R_6 each independently is

1) hydrogen, cyano, nitro, or halo;
2) alkyl;
3) alkenyl;
4) alkynyl;
5) alkoxy;
6) cycloalkyl or heterocyclyl;
7) cycloalkylalkyl or heterocyclylalkyl;
8) aryl or heteroaryl;
9) aralkyl or heteroarylalkyl;
10) $-SO_2R_9$, $-CO_2R_9$, $-SR_9$, or $-SOR_9$; or
11) $-NH_2$, $-NHR_9$, or $-NR_9R_9$;

wherein R_9 is independently H, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl, $-NH_2$, $-NH(C_1\text{-}C_4)$alkyl, $-N[(C_1\text{-}C_4)\text{alkyl}]_2$, $-SO_2$alkyl, $-SO_2$aryl, alkylcarbonyl, alkoxycarbonyl, carbamoyl, urealyl, or carbamyl; and not including 2,3-dithiophen-2-yl-pyrido[2,3-b]pyrazine, 2,3-dithiophen-2-yl-pyrido[2,3-b]pyrazine-6-carboxylic acid (2-morpholin-4-yl-ethyl)-amide; or 2,3-dithiophen-2-yl-pyrido[2,3-b]pyrazine-6-carboxylic acid (3-morpholin-4-yl-propyl)-amide.

Another embodiment of the invention encompasses compounds of Formula (I) wherein R_1 or R_2 are substituted with at least one R_8, wherein R_8 is independently hydroxyl, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl,

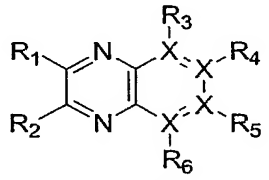
substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl.

Yet another embodiment of the invention encompasses compound of Formula (I) wherein R_1 and R_2 are be taken together to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Another embodiment of the invention encompasses compounds of Formula (I) wherein R_3, R_4, R_5, or R_6 are optionally substituted with R_9, wherein R_9 is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl, $-NH_2$, $-NH(C_1\text{-}C_4)$alkyl, $-N[(C_1\text{-}C_4)\text{alkyl}]_2$, $-SO_2$alkyl, $-SO_2$aryl, alkylcarbonyl, alkoxycarbonyl, carbamoyl, urealyl, or carbamyl.

Yet another embodiment of the invention encompasses compounds of Formula (I) wherein either R_3 and R_4, R_4 and R_5, or R_5 and R_6 are taken together to form a ring including cycloalkyl, heterocyclyl, aryl, or heteroaryl.

Another embodiment of the invention encompasses methods for treating cancer comprising administering a therapeutically effective amount of a compound of Formula (I) to a subject in need of such treatment, wherein the compound has Formula (I):



Formula I

wherein,

X is N or C;

R_1 and R_2 each independently is

1) hydrogen;
2) alkyl;
3) alkoxy;
4) cycloalkyl;
5) heterocyclyl;

6) heterocyclylalkyl;

7) aryl;

8) heteroaryl;

9) aralkyl;

10) heteroaralkyl; or

11) $-NH_2$, $-NHR_8$, or $-NR_8R_8$,

wherein R_8 is independently hydroxyl, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, and optionally, R_1 and R_2 may be taken together to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_3, R_4, R_5, and R_6 each independently is

1) hydrogen, cyano, nitro, or halo;

2) alkyl;

3) alkenyl;

4) alkynyl;

5) alkoxy;

6) cycloalkyl or heterocyclyl;

7) cycloalkylalkyl or heterocyclylalkyl;

8) aryl or heteroaryl;

9) aralkyl or heteroarylalkyl;

10) $-SO_2R_9$, $-CO_2R_9$, $-SR_9$, or $-SOR_9$; or

11) $-NH_2$, $-NHR_9$, or $-NR_9R_9$,

wherein R_9 is independently H, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl, $-NH_2$, $-NH(C_1\text{-}C_4)$alkyl, $-N[(C_1\text{-}C_4)\text{alkyl}]_2$, $-SO_2$alkyl, $-SO_2$aryl, alkylcarbonyl, alkoxycarbonyl, carbamoyl, urealyl, or carbamyl or a pharmaceutically acceptable salt, hydrate or pro-drug thereof, in combination with a pharmaceutically acceptable carrier.

Yet another embodiment of the invention encompasses methods for treating cancer by administering compounds of Formula (I) wherein R_1 or R_2 are substituted with at least one R_8, wherein R_8 is independently hydroxyl, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl.

Another embodiment of the invention encompasses methods for treating cancer by administering compounds of Formula (I) wherein R_1 and R_2 may be taken together to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Yet another embodiment of the invention encompasses methods for treating cancer by administering compounds of Formula (I) wherein R_3, R_4, R_5, or R_6 are optionally substituted with R_9, wherein R_9 is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl, $-NH_2$, $-NH(C_1-C_4)$alkyl, $-N[(C_1-C_4)\text{alkyl}]_2$, $-SO_2$alkyl, $-SO_2$aryl, alkylcarbonyl, alkoxycarbonyl, carbamoyl, urealyl, or carbamyl.

Yet another embodiment of the invention encompasses methods for treating cancer by administering compounds of Formula (I) wherein either R_3 and R_4, R_4 and R_5, or R_5 and R_6 are taken together to form a ring including cycloalkyl, heterocyclyl, aryl, or heteroaryl.

Another embodiment of the invention encompasses methods for treating cancer by administering the compounds of Formula (I) as a dosage form, wherein the dosage form is a tablet, caplet, troche, lozenge, dispersion, suspension, suppository, solution, capsule, or patch. Yet another embodiment of the invention encompasses methods for treating cancer by administering compounds of Formula (I) in an amount of about 0.001 mg/kg to about 100 mg/kg. The compound of Formula (I) may be administered by oral administration.

Detailed Description of the Invention

The present invention encompasses biaryl compounds with two six membered rings fused wherein at least one six membered ring is substituted. The compounds of the invention are useful in the inhibition of PKB kinase, the treatment of cancer, or the inhibition of tumor growth. In particular, the compounds of the invention encompass substituted or unsubstituted quinoxalinyl or, pyridopyrazinyl compounds. The invention also encompasses methods for treating cancer by administering to a subject in need thereof, a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

Definitions

As used herein, the term "alkyl" refers to a saturated hydrocarbon radical having 1 to 8 carbon atoms. The alkyl group may be straight, branched, substituted or unsubstituted. Alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, or t-butyl.

As used herein, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, which may be straight chain or branched, substituted or unsubstituted, having from 2 to 8 carbon atoms and at least one carbon to carbon double bond. Alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, or 2-methylbutenyl.

As used herein, the term "alkynyl" as used herein refers to a hydrocarbon radical, which may be straight chained or branched, substituted or unsubstituted, having 2 to 8 carbon atoms and at least one carbon to carbon triple bond. Alkynyl groups include, but are not limited to, ethynyl, propynyl, or butynyl.

As used herein, the term "alkoxy" refers to a substituted or unsubstituted an -O-alkyl, -O-alkenyl, -O-alkynyl group, -O-cycloalkyl, or -O-heterocyclyl, wherein alkyl, alkenyl, and alkynyl are as defined above and cycloalkyl and heterocyclyl are as defined below. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy, allyloxy, propargyloxy, or vinyloxy.

As used herein, the term "cycloalkyl" refers to a cyclic hydrocarbon radical having 3 to 8 carbon atoms, which may be substituted or unsubstituted. Optionally, the cycloalkyl group may have at least one carbon to carbon double bond. Cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, or cyclohexyl.

As used herein, the term "heterocyclyl" or "heterocycle" refers to cycloalkyl rings that include within the ring at least one nitrogen, oxygen, or sulfur atom. Optionally, the heterocyclyl may include one or two double bonds. The nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The term "heterocyclyl" also refers to dihydro and tetrahydro analogs of heteroaryls. The heterocyclic ring may be attached at any heteroatom or carbon atom, which results in the creation of a stable structure. The heterocycle ring can be substituted or unsubstituted including, but not limited to, aziridinyl, homopiperazinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholino, oxadiazolyl, oxazolidinyl, oxazolinyl, 4-piperidonyl, piperazinyl, pyranyl, pyradazinyl, pyrazolidinyl, pyrrolidinyl, quinuclidinyl, tertrahydrofuranyl, tetrahydrothienyl, tetrahydrothiophenyl, thiazolidinyl, thiazolinyl, thiomorpholino, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, or thiophenyl.

As used herein, the term "aryl" refers to carbocyclic aromatic groups including, but not limited to, phenyl, naphthyl, or anthracyl. The term "aryl" also refers to any bicyclic group in which a cycloalkyl or heterocyclyl ring is fused to a benzene ring, examples include, but are not limited to, benzimidazolyl, benzofuranyl, benzoisothiazolyl, benzoisoxazolyl, benzooxazolyl, benzopyranyl, benzothiazolyl, benzothienyl, benzotriazole, benzoxazolyl, indolinyl, indolizinyl, indolyl, isoindolyl, isoquinolinyl, or quinolinyl. An aryl ring may be unsubstituted or substituted with at least one suitable substituent.

As used herein the term "heteroaryl" refers to a monocyclic or polycyclic aromatic ring comprising carbon atoms, hydrogen atoms, and at least one heteroatom, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur. The nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The term "heteroaryl" includes, but is not limited to, azepinyl, benzimidazoyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, isoimidazolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiadiazoyl, thiazolyl, thienyl, triazinyl, 1,2,3-triazolyl, or 1,2,4-triazolyl. A heteroaryl group can be unsubstituted or substitued.

As used herein, the term "cycloalkylalkyl" refers to a straight-chain alkyl, alkenyl or alkynyl group wherein one of the hydrogen atoms bonded to a terminal carbon is replaced with a cycloalkyl moiety, for example, $-(CH_2)_n$-cycloalkyl, wherein n = 1-6.

As used herein, the term "heterocyclylalkyl" refers to a straight-chain alkyl, alkenyl or alkynyl group wherein one of the hydrogen atoms bonded to a terminal carbon is replaced with a heterocyclyl moiety, for example, -$(CH_2)_n$-heterocyclyl, wherein n = 1-6.

As used herein, the term "aralkyl" refers to a straight-chain alkyl, alkenyl, or alkynyl group wherein one of the hydrogen atoms bonded to a terminal carbon is replaced with an aryl moiety. Typical aralkyl groups include, but are not limited to, benzyl, benzylidene, benzylidyne, benzenobenzyl, naphthenobenzyl, and the like.

As used herein, the term "heteroaralkyl" refers to a straight-chain alkyl, alkenyl, or alkynyl group wherein one of the hydrogen atoms bonded to a terminal carbon is replaced with a heteroaryl moiety.

As used herein, the term "aryloxy group" refers to an -O-aryl or -O-heteroaryl, wherein aryl or heteroaryl is as defined above. An aryloxy group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the aryl ring of an aryloxy group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)aryloxy."

As used herein, the term "carbonyl" refers to a divalent group of the formula -CO-, which is also referred to as oxo.

As used herein, the term "alkylcarbonyl" refers a monovalent group of the formula -CO-alkyl. Preferably, the hydrocarbon chain of an alkylcarbonyl group is C_1-C_8 atoms in length, referred to herein as a "lower alkylcarbonyl" group.

As used herein, the term "arylcarbonyl" refers to a monovalent group of the formula -CO-aryl or -CO-aralkyl, wherein the aryl is optionally substituted with a suitable substituent.

As used herein, the term "alkoxycarbonyl" refers to a monovalent group of the formula -CO-alkoxy. Preferably, the hydrocarbon chain of an alkoxycarbonyl group is C_1-C_8 atoms in length, referred to herein as a "lower alkoxycarbonyl" group.

As used herein, the term "carbamoyl" refers to a radical -CON(R)- or -(R)NCO-, wherein R wherein R is further defined herein.

As used herein, the term "urea" or "urealyl" refers to a radical -RNHCONR-, wherein R may be the same or different is further defined herein.

As used herein, the term "carbamic acid" or "carbamyl" refers to a radical -RNHCOO-, wherein R is further defined herein.

As used herein, a "suitable substituent" means a group that does not nullify the synthetic or pharmaceutical utility of the compounds of the invention or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to: C_1-C_8 alkyl; C_2-C_8 alkenyl; C_2-C_8 alkynyl; C_6 aryl; C_2-C_5 heteroaryl; C_3-C_7 cycloalkyl; C_1-C_8 alkoxy; C_6 aryloxy; -CN; -OH; oxo; halo; $-CO_2H$; $-NH_2$; $-NH(C_1$-C_8 alkyl); $-N(C_1$-C_8 alkyl)$_2$; $-NH(C_6$ aryl); $-N(C_6$ aryl)$_2$; -CHO; $-CO(C_1$-C_8 alkyl); $-CO(C_6$ aryl); $-CO_2(C_1$-C_8 alkyl); and $-CO_2(C_6$ aryl). One of skill in art can readily choose a suitable substituent based on the stability and pharmacological and synthetic activity of the compound of the invention.

As used herein, the term "halo" or "halogen" includes fluorine, chlorine, bromine, or iodine, including fluoro, chloro, bromo, and iodo.

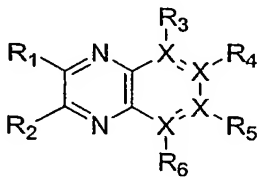
When one or more chiral centers are present in the compounds of the present invention, the individual isomers, *i.e.*, enantiomers, diastereomers, etc. and mixtures thereof (*e.g.*, racemates, etc.) are intended to be encompassed by the formulae depicted herein. Also included are individual polymorphs of each compound of the present invention.

As used herein the terms "pharmaceutically acceptable salts" and "hydrates" refer to those salts and hydrated forms of the compound that would be apparent to those in the art, *i.e.*, those which favorably affect the physical or pharmacokinetic properties of the compound, such as solubility, palatability, absorption, distribution, metabolism, and excretion. Other factors, more practical in nature, which those skilled in the art may take into account in the selection include the cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity, and flowability of the resulting bulk drug. Pharmaceutically acceptable salts may be prepared by the addition of an appropriate acid. Thus, the compound can be used in the form of salts derived from inorganic or organic acids. Examples include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, pamoate, pectinate, persulfate, 3-phenylpropionate, pivalate, propionate, succinate, tartrate, or undecanoate.

As used herein, the term "subject" refers to a mammal, preferably a human, but can also be an animal in need of veterinary treatment.

One embodiment of the invention encompasses biaryl compounds with two six membered rings fused wherein the pyrazine ring is substituted and useful in the inhibition of PKB kinase. In particular, the compounds of the invention encompass substituted or unsubstituted quinoxalinyl or, pyridopyrazinyl compounds. Generally, the compounds of the invention are represented in Formula (I):

wherein,



Formula I

X is N or C;

R_1 and R_2 each independently is

1) hydrogen;

2) alkyl, optionally substituted with R_8;

3) alkoxy, optionally substituted with R_8;

4) cycloalkyl, optionally substituted with at least one R_8;

5) heterocyclyl, optionally substituted with at least one R_8;

6) cylcoalkylalkyl or heterocyclylalkyl, optionally substituted with at least one R_8;

7) aryl, optionally substituted with at least one R_8;

8) heteroaryl, optionally substituted with at least one R_8;

9) aralkyl, optionally substituted with at least one R_8;

10) heteroaralkyl, optionally substituted with at least one R_8; or

11) $-NH_2$, $-NHR_8$, or $-NR_8R_8$;

wherein both R_1 and R_2 are not hydrogen, R_8 is independently cyano, hydroxyl, halo, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl, and optionally, R_1 and R_2 may be taken together to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_3, R_4, R_5, and R_6 each independently is

1) hydrogen, cyano, nitro, or halo;

2) alkyl, optionally substituted with at least one R_9;

3) alkenyl, optionally substituted with at least one R_9;

4) alkynyl, optionally substituted with at least one R_9;

5) alkoxy, optionally substituted with at least one R_9;

6) cycloalkyl or heterocyclyl, optionally substituted with at least one R_9;

7) cycloalkylalkyl or heterocyclylalkyl, optionally substituted with at least one R_9;

8) aryl or heteroaryl, optionally substituted with at least one R_9;

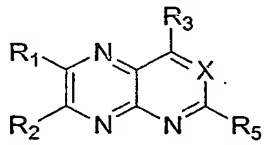
9) aralkyl or heteroarylalkyl, optionally substituted with at least one R_9;

10) $-SO_2R_9$, $-CO_2R_9$, $-SR_9$, or $-SOR_9$; or

11) $-NH_2$, $-NHR_9$, or $-NR_9R_9$,

wherein R_9 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaralkyl, $-NH_2$, $-NH(C_1\text{-}C_4)$alkyl, $-N[(C_1\text{-}C_4)\text{alkyl}]_2$, $-SO_2$alkyl, $-SO_2$aryl, alkylcarbonyl, alkoxycarbonyl, carbamoyl, urealyl, or carbamyl, or optionally, either R_3 and R_4, R_4 and R_5, or R_5 and R_6 are taken together to form a ring including cycloalkyl, heterocyclyl, aryl, or heteroaryl; and not including 2,3-dithiophen-2-yl-pyrido[2,3-b]pyrazine, 2,3-dithiophen-2-yl-pyrido[2,3-b]pyrazine-6-carboxylic acid (2-morpholin-4-yl-ethyl)-amide; or 2,3-dithiophen-2-yl-pyrido[2,3-b]pyrazine-6-carboxylic acid (3-morpholin-4-yl-propyl)-amide.

The invention also encompasses compounds of Formula II:



Formula II

wherein,

X is N or C-R_4;

R_1 and R_2 each independently is

1) C_1-C_8 alkyl, optionally substituted with R_8;

2) C_1-C_8 alkoxy, optionally substituted with R_8;

3) C_3-C_8 cycloalkyl, optionally substituted with at least one R_8;

4) C_3-C_8 heterocyclyl, optionally substituted with at least one R_8;

5) C_3-C_8 cycloalkylalkyl or heterocyclylalkyl, optionally substituted with at least one R_8;

6) C_5-C_{10} aryl, optionally substituted with at least one R_8;

7) C_4-C_{10} heteroaryl, optionally substituted with at least one R_8;

8) C_6-C_{14} aralkyl, optionally substituted with at least one R_8;

9) C_5-C_{14} heteroaralkyl, optionally substituted with at least one R_8; or

10) $-NH_2$, $-NHR_8$, or $-NR_8R_8$,

wherein R_8 is independently hydroxyl, halo, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-NH_2$, $-NHR_{12}$, or $-NR_{12}R_{12}$, wherein R_{12} is alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; and optionally, R_1 and R_2 may be taken together to form a substituted or unsubstituted C_5-C_8 cycloalkyl, C_4-C_8 heterocyclyl, C_5-C_8 aryl, or C_4-C_8 heteroaryl;

R_3 and R_5 each independently is

1) hydrogen, halo, cyano, or nitro;

2) C_1-C_8 alkyl, optionally substituted with at least one R_9;

3) C_2-C_8 alkenyl, optionally substituted with at least one R_9;

4) C_2-C_8 alkynyl, optionally substituted with at least one R_9;

5) C_1-C_8 alkoxy, optionally substituted with at least one R_9;

6) C_3-C_8 cycloalkyl or heterocyclyl, optionally substituted with at least one R_9;

7) C_4-C_8 cycloalkylalkyl or heterocyclylalkyl, optionally substituted with at least one R_9;

8) C_3-C_{10} aryl or heteroaryl, optionally substituted with at least one R_9;

9) C_6-C_{14} aralkyl or heteroaralkyl, optionally substituted with at least one R_9; or

10) $-CO_2R_9$, $-SR_9$, $-SOR_9$, or $-SO_2R_9$;

wherein R_9 is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, C_5-C_6 heterocyclyl, C_5-C_8 aryl, C_3-C_8 heteroaryl, C_6-C_{10} aralkyl, or C_5-C_{10} heteroaralkyl, and optionally, either R_3 and R_4, R_4 and R_5, or R_5 and R_6 are taken together to form a ring including C_4-C_6 cycloalkyl, C_4-C_6 heterocyclyl, C_5-C_8 aryl, or C_3-C_8 heteroaryl; and

R_4 is

1) cyano, nitro, or halo;

2) C_1-C_8 alkyl, optionally substituted with at least one R_{10};

3) C_2-C_8 alkenyl, optionally substituted with at least one R_{10};

4) C_1-C_8 alkoxy, optionally substituted with at least one R_{10};

5) C_3-C_8 cycloalkyl, optionally substituted with at least one R_{10};

6) C_3-C_8 heterocyclyl, optionally substituted with at least one R_{10};

7) C_5-C_8 aryl, optionally substituted with R_{10};

8) C_3-C_{10} heteroaryl, optionally substituted with R_{10};

9) C_5-C_8 cycloalkylalkyl, optionally substituted with at least one R_{10};

10) C_5-C_8 heterocyclylalkyl, optionally substituted with at least one R_{10};

11) C_6-C_8 aralkyl, optionally substituted with at least one R_{10};

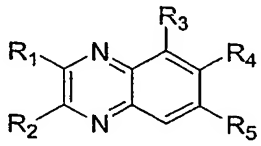
12) C_5-C_8 heteroaralkyl, optionally substituted with at least one R_{10};

13) $-CO_2R_{10}$, $-SR_{10}$, $-SOR_{10}$, or $-SO_2R_{10}$; or

14) $-NH_2$, $-NHR_{10}$, or $-NR_{10}R_{10}$,

wherein R_{10} is independently H, C_1-C_4 alkyl, C_2-C_4 alkenyl optionally subsituted with R_{13}, C_1-C_4 alkoxy optionally subsituted with R_{13}, C_4-C_6 heterocyclyl optionally subsituted with R_{13}, C_4-C_{10} heterocyclylalkyl optionally subsituted with R_{13}, C_7-C_8 aralkyl optionally substituted with R_{13}, C_5-C_8 heteroaralkyl optionally substituted with R_{13}, NH_2, NHR_{13}, $NR_{13}R_{13}$, $-SO_2R_{13}$, C_1-C_5 carbomoyl optionally substituted with R_{13}, C_2-C_5 alkylcarbonyl optionally substituted with R_{13}, or C_2-C_5 alkoxycarbonyl optionally substituted with R_{13}, wherein R_{13} is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_6-C_{10} aryl, C_5-C_8 heterocyclylalkyl, $-SO_2R_{14}$, C_2-C_6 alkylcarbonyl optionally substituted with R_{14}, C_6-C_{10} arylcarbonyl optionally substituted with R_{14}, carbamoyl, urealyl, or carbamyl, wherein R_{14} is C_1-C_4 alkyl, C_1-C_4 alkoxy, aryl, arylcarbonyl, NH_2, $NH[(C_1$-$C_4)alkyl]$, $N[(C_1$-$C_4)alkyl]_2$, alkylcarbonyl, alkoxycarbonyl, carbamoyl, urealyl, or carbamyl; and not including 2,3-dithiophen-2-yl-pyrido[2,3-b]pyrazine.

The invention also encompasses compounds having Formula III:



Formula III

wherein,

R_1 and R_2 each independently is

1) hydrogen;

2) C_1-C_8 alkyl, optionally substituted with R_8;

3) C_1-C_8 alkoxy, optionally substituted with R_8;

4) C_3-C_8 cycloalkyl, optionally substituted with at least one R_8;

5) C_3-C_8 heterocyclyl, optionally substituted with at least one R_8;

6) C_3-C_8 cycloalkylalkyl or heterocyclylalkyl, optionally substituted with at least one R_8;

7) C_5-C_{10} aryl, optionally substituted with at least one R_8;

8) C_3-C_{10} heteroaryl, optionally substituted with at least one R_8;

9) C_6-C_{14} aralkyl, optionally substituted with at least one R_8;

10) C_5-C_{14} heteroaralkyl, optionally substituted with at least one R_8; or

11) $-NH_2$, $-NHR_8$, or $-NR_8R_8$,

wherein both R_1 and R_2 are not hydrogen, R_8 is independently hydroxyl, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-NH_2$, $-NHR_{12}$, $-NR_{12}R_{12}$, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, urealyl, carbamyl, $-SO_2R_{12}$, wherein R_{12} is halo, cyano, hydroxyl, C_1-C_4 alkyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, aryl, NH_2, $NH[(C_1$-$C_4)alkyl]$, $N[(C_1$-$C_4)alkyl]_2$; or optionally, R_1 and R_2 may be taken together to form a substituted or unsubstituted C_4-C_8 cycloalkyl, C_4-C_8 heterocyclyl, C_5-C_8 aryl, or C_5-C_8 heteroaryl; and

R_3, R_4, and R_5 each independently is

1) hydrogen, halo, cyano, or nitro;

2) C_1-C_8 alkyl, optionally substituted with at least one R_9;

3) C_2-C_8 alkenyl, optionally substituted with at least one R_9;

4) C_2-C_8 alkynyl, optionally substituted with at least one R_9;

5) C_1-C_8 alkoxy, optionally substituted with at least one R_9;

6) C_3-C_8 cycloalkyl or heterocyclyl, optionally substituted with at least one R_9;

7) C_5-C_8 aryl, optionally substituted with at least one R_9;

8) C_3-C_{10} heteroaryl, optionally substituted with at least one R_9;

9) C_6-C_{14} aralkyl, optionally substituted with at least one R_9;

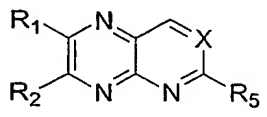
10) $-NH_2$, $-NHR_9$, or $-NR_9R_9$; or

11) C_2-C_{10} carbamoyl, optionally substituted with at least one R_9;

wherein R_9 is independently C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, C_5-C_6 heterocyclyl, C_5-C_8 aryl, C_3-C_{10} heteroaryl, C_6-C_{10} aralkyl, C_4-C_{10} heteroarylalkyl, C_5-C_8 aryloxy, alkylcarbonyl, arylcarbonyl, carbamoyl, carbamyl,

urealyl, or $-SO_2R_{11}$ wherein R_{11} is F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_5-C_8 aryl, C_4-C_8 heteroaryl, or optionally, either R_3 and R_4, or R_4 and R_5 are taken together to form a C_4-C_6 cycloalkyl, C_4-C_6 heterocyclyl, or C_5-C_8 aryl.

In a more preferred embodiment, the compounds of the invention have Formula IIA:



Formula IIA

wherein,

X is N or C-R_4;

R_1 or R_2 each independently is

1) C_6-C_{10} aryl, optionally substituted with R_8;

2) C_4-C_{10} heteroaryl, optionally substituted with R_8; or

wherein R_8 is F, Cl, Br, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, NH_2, NHR_{12}, or $NR_{12}R_{12}$, wherein R_{12} is independently C_1-C_4 alkyl;

R_5 is

1) hydrogen, F, Cl, or Br;

2) C_1-C_8 alkyl, optionally substituted with at least one R_9;

3) C_1-C_8 alkoxy, optionally substituted with at least one R_9;

4) C_3-C_8 cycloalkyl or heterocyclyl, optionally substituted with at least one R_9;

5) C_3-C_{10} aryl or heteroaryl, optionally substituted with at least one R_9; or

6) C_6-C_{14} aralkyl, optionally substituted with at least one R_9,

wherein R_9 is independently C_1-C_4 alkyl, C_1-C_4 alkoxy, C_5-C_8 aryl, or C_4-C_8 heteroaryl; and

R_4 is

1) F, Cl, Br, or cyano;

2) C_1-C_8 alkyl, optionally substituted with at least one R_{10};

3) C_1-C_8 alkoxy, optionally substituted with at least one R_{10};

4) C_3-C_8 cycloalkyl, optionally substituted with at least one R_{10};

5) C_3-C_8 heterocyclyl, optionally substituted with at least one R_{10};

6) C_5-C_8 aryl, optionally substituted with R_{10};

7) C_3-C_{10} heteroaryl, optionally substituted with R_{10}; or

8) $-NH_2$, $-NHR_{10}$, or $-NR_{10}R_{10}$,

wherein R_{10} is independently C_1-C_4 alkyl, C_1-C_4 alkoxy, C_4-C_6 heterocyclyl optionally substituted with R_{13}, C_4-C_{10} heterocyclylalkyl optionally substituted with R_{13}, C_7-C_8 aralkyl optionally substituted with R_{13}, C_5-C_8 heteroaralkyl optionally substituted with R_{13}, NH_2, $NH[(C_1$-$C_4)alkyl]$, $N[(C_1$-$C_4)alkyl]_2$, $-SO_2R_{13}$, C_1-C_5 carbomoyl optionally substituted with R_{13}, C_2-C_5 alkylcarbonyl optionally substituted with R_{13}, wherein R_{13} is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_6-C_{10} aryl, C_2-C_6 alkylcarbonyl, C_6-C_{10} arylcarbonyl, $-NH_2$, $NH[(C_1$-$C_4)alkyl]$, $N[(C_1$-$C_4)alkyl]_2$, C_2-C_6 alkoxycarbonyl, C_1-C_6 carbamoyl, C_1-C_6 urealyl, or C_1-C_6 carbamyl.

In a most preferred embodiment, the compounds of the invention have Formula IIA wherein,

X is N or C-R_4;

R_1 or R_2 each independently is

1) thienyl, optionally substituted with R_8; or

2) furanyl, optionally substituted with R_8;

wherein R_8 is F, Cl, Br, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, NH_2, NHR_{12}, or $NR_{12}R_{12}$, wherein R_{12} is independently C_1-C_4 alkyl;

R_5 is

1) hydrogen;

2) C_1-C_8 alkyl, optionally substituted with at least one R_9; or

3) C_1-C_8 alkoxy, optionally substituted with at least one R_9;

wherein R_9 is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_5-C_8 aryl, or C_4-C_8 heteroaryl; and

R_4 is

1) F, Cl, Br, or cyano;

2) C_1-C_8 alkyl, optionally substituted with at least one R_{10};

3) C_1-C_8 alkoxy, optionally substituted with at least one R_{10};

4) C_3-C_8 cycloalkyl, optionally substituted with at least one R_{10};

5) C_3-C_8 heterocyclyl, optionally substituted with at least one R_{10};

6) C_5-C_8 aryl, optionally substituted with R_{10};

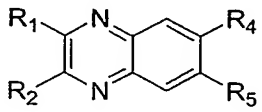
7) C_3-C_{10} heteroaryl, optionally substituted with R_{10}; or

8) $-NH_2$, $-NHR_{10}$, or $-NR_{10}R_{10}$,

wherein R_{10} is independently C_1-C_4 alkyl, C_1-C_4 alkoxy, C_4-C_6 heterocyclyl optionally substituted with R_{13}, C_7-C_8 heterocyclylalkyl optionally substituted with R_{13}, C_7-C_8 aralkyl optionally substituted with R_{13}, C_5-C_8 heteroaralkyl optionally substituted with R_{13}, NH_2, $NH[(C_1$-$C_4)alkyl]$, $N[(C_1$-$C_4)alkyl]_2$, $-SO_2R_{13}$, C_1-C_5 carbamoyl optionally

substituted with R_{13}, C_2-C_5 alkylcarbonyl optionally substituted with R_{13}, wherein R_{13} is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_6-C_{10} aryl, C_2-C_6 alkylcarbonyl, C_6-C_8 arylcarbonyl, -NH_2, NH[(C_1-C_4)alkyl], N[(C_1-C_4)alkyl]$_2$, C_2-C_6 alkoxycarbonyl, C_1-C_6 carbamoyl, C_1-C_6 urealyl, or C_1-C_6 carbamyl.

In a more preferred embodiment, the compounds of the invention have Formula IIIA:



Formula IIIA

wherein,

R_1 and R_2 each independently is

1) hydrogen;

2) C_3-C_8 heterocyclyl, optionally substituted with at least one R_8;

3) C_5-C_{10} aryl, optionally substituted with at least one R_8;

4) C_3-C_{10} heteroaryl, optionally substituted with at least one R_8;

5) C_5-C_{14} heteroaralkyl, optionally substituted with at least one R_8; or

6) -NH_2, -NHR_8, or -NR_8R_8,

wherein both R_1 and R_2 may not be hydrogen, R_8 is hydroxyl, C_1-C_4 alkyl optionally substituted with R_{12}, C_5-C_{10} aryl optionally substituted with R_{12}, C_5-C_{10} heteroaryl, C_6-C_{10} aralkyl, C_6-C_{10} heteroaralkyl, -NH_2, -NHR_{12}, -$NR_{12}R_{12}$, wherein R_{12} is F, Cl, Br, cyano, hydroxyl, C_1-C_4 alkyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, -NH_2, -NH[(C_1-C_4)alkyl], N[(C_1-C_4)alkyl]$_2$; and

R_4 or R_5 each independently is

1) hydrogen, F, Cl, or Br;

2) C_1-C_8 alkyl, optionally substituted with at least one R_9;

3) C_1-C_8 alkoxy, optionally substituted with at least one R_9;

4) C_5-C_8 aryl, optionally substituted with at least one R_9;

5) -NH_2, -NHR_9, or -NR_9R_9; or

6) C_2-C_{10} carbamoyl, optionally substituted with at least one R_9;

wherein R_9 is independently C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl optionally substituted with R_{11}, C_5-C_6 heterocyclyl optionally substituted with R_{11}, C_5-C_8 aryl optionally substituted with R_{11}, C_3-C_{10} heteroaryl optionally substituted with R_{11}, C_6-C_{10} aralkyl, C_4-C_{10} heteroarylalkyl optionally substituted with R_{11}, C_2-C_{10}

alkylcarbonyl, C_7-C_{10} arylcarbonyl, C_2-C_8 carbamoyl optionally substituted with R_{11}, C_2-C_8 carbamyl optionally substituted with R_{11}, C_2-C_8 urealyl optionally substituted with R_{11}, or $-SO_2R_{11}$, wherein R_{11} is F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_5-C_8 aryl, or C_4-C_8 heteroaryl optionally substituted with F, Cl, Br, cyano, C_1-C_4 alkyl, or C_1-C_4 alkoxy.

In a most preferred embodiment, the compounds of the invention have Formula IIIA wherein,

R_1 or R_2 each independently is

1) hydrogen;

2) thienyl, optionally substituted with R_8;

3) furanyl, optionally substituted with R_8;

4) C_3-C_8 heterocyclyl, optionally substituted with at least one R_8;

5) C_5-C_{14} heteroaralkyl, optionally substituted with at least one R_8; or

6) $-NH_2$, $-NHR_8$, or $-NR_8R_8$,

wherein both R_1 and R_2 may not be hydrogen, R_8 is hydroxyl, C_1-C_4 alkyl optionally substituted with R_{12}, C_5-C_{10} aryl optionally substituted with R_{12}, C_5-C_{10} heteroaryl, C_6-C_{10} aralkyl, C_6-C_{10} heteroaralkyl, $-NH_2$, $-NHR_{12}$, or $-NR_{12}R_{12}$, wherein R_{12} is F, Cl, Br, cyano, hydroxyl, C_1-C_4 alkyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, $-NH_2$, $-NH[(C_1$-$C_4)alkyl]$, or $-N[(C_1$-$C_4)alkyl]_2$; and

R_4 or R_5 each independently is

1) hydrogen, F, Cl, or Br;

2) C_1-C_8 alkyl, optionally substituted with at least one R_9;

3) C_1-C_8 alkoxy, optionally substituted with at least one R_9;

4) C_5-C_8 aryl, optionally substituted with at least one R_9;

5) $-NH_2$, $-NHR_9$, or $-NR_9R_9$; or

6) C_2-C_{10} carbamoyl, optionally substituted with at least one R_9;

wherein R_9 is independently C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl optionally substituted with R_{11}, C_5-C_6 heterocyclyl optionally substituted with R_{11}, C_5-C_8 aryl optionally substituted with R_{11}, C_3-C_{10} heteroaryl optionally substituted with R_{11}, C_6-C_{10} aralkyl optionally substituted with R_{11}, C_4-C_8 heteroarylalkyl optionally substituted with R_{11}, C_2-C_{10} alkylcarbonyl, C_7-C_{10} arylcarbonyl, C_2-C_8 carbamoyl optionally substituted with R_{11}, C_2-C_6 carbamyl optionally substituted with R_{11}, C_2-C_6 urealyl optionally substituted with R_{11}, or $-SO_2R_{11}$, wherein R_{11} is F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_5-C_8 aryl, or C_4-C_8 heteroaryl optionally substituted with F, Cl, Br, cyano, C_1-C_4 alkyl, or C_1-C_4 alkoxy.

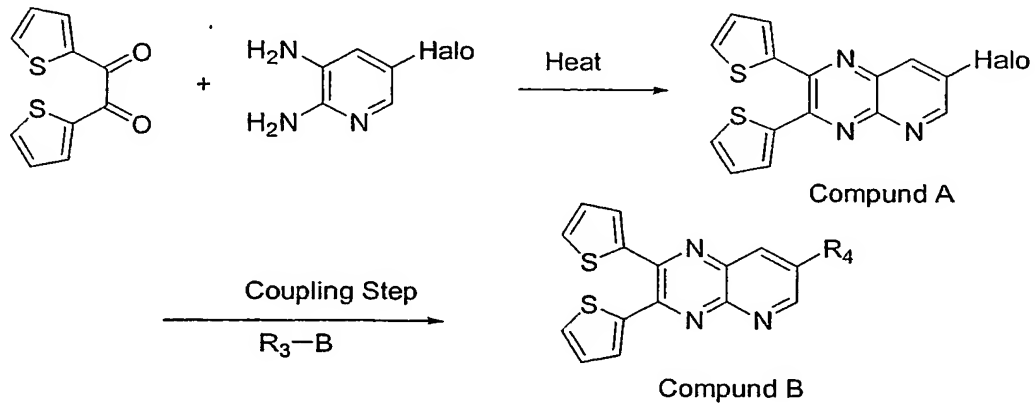
In a more preferred embodiment, the compounds of the invention include compounds having Formula IIIA, wherein at least one of R_1 or R_2 is not hydrogen.

Compounds of Formula I wherein the six membered ring is pyridine or pyrimidine are made using the synthetic pathways illustrated in Schemes 1, 2, and 3. Although the schemes illustrate a six membered ring with one substitution, methodologies to introduce a second or third substitution are well within the abilities of the ordinary skilled artisan. The reactions may be carried out consecutively, *i.e.*, with intervening isolation and/or purification steps, or concurrently, *i.e.*, the reaction mixture is carried forth in the reaction sequence without isolation and/or purification. Starting materials useful for the preparing the compounds of the invention and intermediates therefor, are commercially available or can be prepared by well know synthetic methods.

The compounds of the invention are synthesized using a variety of schemes, such as those illustrated below and exemplified in the Example section. One of ordinary skill in the art readily understands that reaction conditions may vary slightly due to specific reactants, when necessary the compounds may use protecting groups, or that more than one substituent may be included in the reaction. Although, the following schemes are exemplified using thiophene for R_1 and R_2, one of ordinary skill in the art can easily alter the reagents and reaction conditions to with little or no experimentation include the groups defined above for R_1 and R_2.

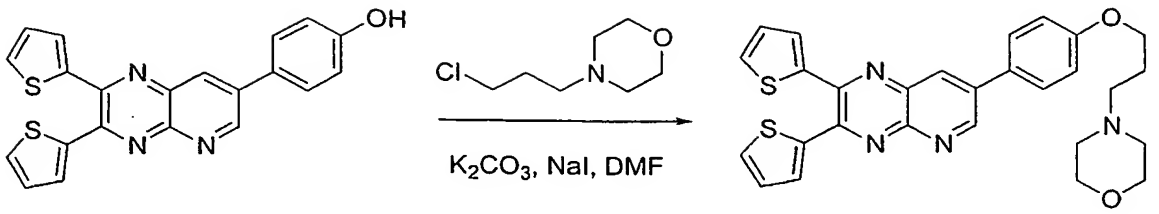
Compounds of Formula II may be synthesized in at least two ways as illustrated by Schemes 1-3. Scheme 1 illustrates one method to synthesize compounds having a pyridopyrazine ring system. A diketodiaryl compound is reacted with a halo substituted diamino pyridine at a high temperature, *e.g.* 100°C, in an organic solvent to obtain the 2,3-diarylpyridopyrazine compound (Compound A). Suitable reaction conditions are generally illustrated by Weimann *et al.*, and Sakata *et al.* See, "Synthesis of Heterocyclic Compounds with Pyrazine Nuclei," Weimann, *et al. Comptes Rendus des Seances de l'Academie des Sciences, Serie C: Sciences Chimiques*, 263, 608-611 (1966); and Sakata *et al.*, "Recent Progress in the Quinoxaline Chemistry. Synthesis and Biological Activity," *Heterocycles*, 27, 2481-2515 (1988). Suitable organic solvents include those that may be heated to a temperature of about 35°C to about 110°C without reacting with the reactants. Alternatively, the reaction may be conducted without solvent. Suitable organic solvents include, but are not limited to, alcohols, ethers, hydrocarbons, aromatics, or heterocyclics. Preferably, the solvents include, but are not limited to, ethanol, dioxane,

benzene, toluene, tetrahydrofuran, 1-methyl-pyrrolidine, N,N-dimethylforamide, dimethylsulfoxide. Thereafter, the halo group of Compound A may be substituted using a coupling step to obtain Compound B. Typically, the coupling step is performed using a palladium catalyst and a boronic acid or ester compound in an inert solvent. Such coupling reactions are generally described by Kotha, *et al.* "Recent Applications of the Suzuki-Miyaura Cross-Coupling Reaction in Organic Synthesis," *Tetrahedron*, 58, 9633-9695 (2002). Typically, coupling catalysts include, but are not limited to, palladium halides, palladium phosphine, or silver or nickel ions. Preferably, the coupling catalysts include $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)$, or $Pd(PPh_3)_4$. Typically boronic acid compounds include, but are not limited to, 2-thiopheneboronic acid, 4-hydroxyphenylboronic acid, 4-carboxaldehyde-2-thiopheneboronic acid, halo-substituted phenylboronic acid, amino-substituted phenylboronic acid, or carboxyl-substituted phenylboronic acid. The coupling step, however, is not only limited to palladium catalyzed boronic acid coupling, other coupling reactions which may be suitable include palladium-amination, nickel catalyzed aryl couplings, or silver promoted coupling.



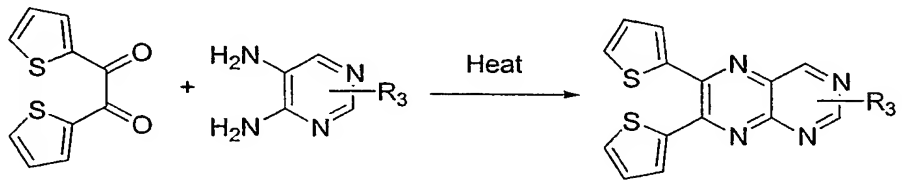
Scheme 1

The position at R_4 may be further functionalized as exemplified in Scheme 2. R_4 may include a functional group capable of further derivatization such as amide, amine, carboxylic acid, cyano, ester, halo, hydroxyl, nitro, sulfone, sulfoxide, thiol, etc. For example, in Scheme 2, R_4, represented by 4-hydroxylphenyl, is alkylated with N-(3-chloropropyl)morpholine under basic conditions in an inert organic solvent. Suitable bases for the reaction include, but are not limited to, carbonates, bicarbonates, hydroxides, fluorides, oxides, hydrides, amides, or alkyl lithium reagents.



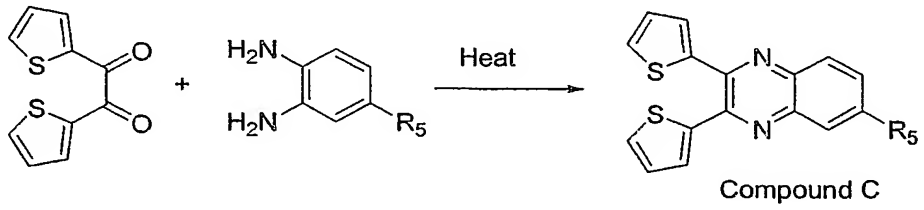
Scheme 2

Compounds of Formula II having a pteridine ring system may be synthesized by reacting a diaryldiketo compound with a substituted or unsubstituted 4,5-diaminopyrimidine while heating in an inert organic solvent. See, Scheme 3. Temperatures and solvents such as those described for Scheme 1 may be used. Although the compounds exemplified are monosubstituted with R_3, one of ordinary skill in the art readily understands that a substituent may be incorporated at either or both carbons of the pyrimidine ring.



Scheme 3

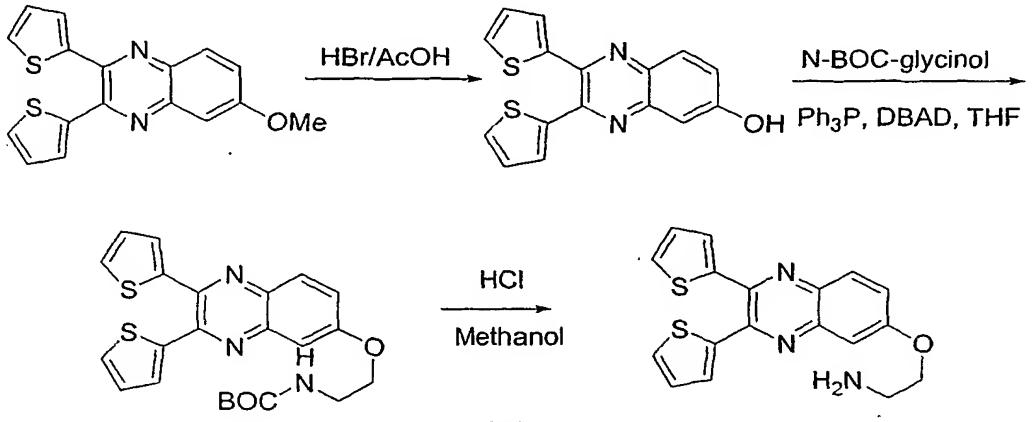
The compounds of Formula III, wherein the ring system is a substituted or unsubstituted quinoxaline may be synthesized as illustrated in Schemes 4 and 5 and exemplified in the examples. The diketoaryl compound is allowed to react with 4-substituted-2-aminoaniline while heating in an inert organic solvent to obtain Compound C.



Scheme 4

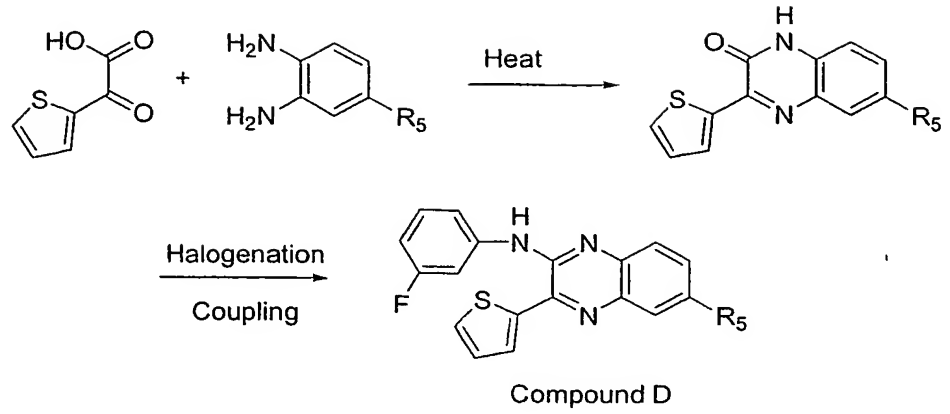
As discussed above for R_4, R_5 may be a substituent capable of further functionalization such as illustrated in Scheme 5. Substituents capable of further functionalization include, but are not limited to, amide, amine, carboxylic acid, cyano, ester, halo, hydroxyl, nitro, sulfone, sulfoxide, thiol, etc. Further functionalization of

substituents is well within one of ordinary skill in the art, for example, alkylation, amidation, coupling, oxidation, reduction, esterification, etc. See generally, D. L. Hughes, "Progress in the Mitsonubu Reaction. A review," Organic Preparations and Procedures International, 28, 127-164 (1996). If necessary, protection groups may be used such as those described by Theodora W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, New York (1981). In Scheme 5, a methyl ether is hydrolyzed to yield the alcohol, which is alkylated with a protected alkylamine, as catalyzed by PPh_3 and di-*tert*-butylazodicarboxylate (DBAD). Thereafter, the BOC group is removed under acidic conditions.



Scheme 5

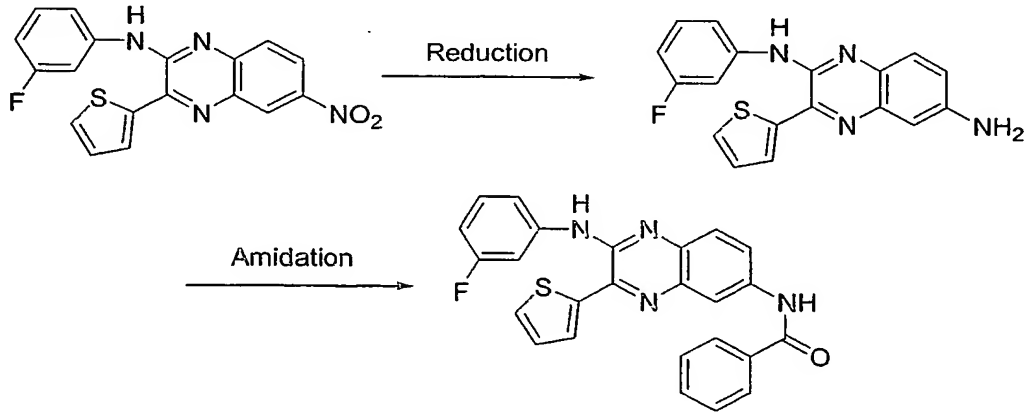
Scheme 6 illustrates a synthetic pathway to obtain compounds of the invention wherein the aryl groups of R_1 and R_2 are not the same. The 2-aryloxoacetic ester is reacted with a 4-substituted-2-aminoaniline and the resulting quinoxolone is converted into a halide and displaced with a substituted aniline while heating in an inert organic solvent to yield Compound D. For exemplary reaction conditions see Badr, *et al.*, "Reaction of Quinoxaline Derivatives with Nucleophilic Reagents." *Bull. Chem. Soc. Japan*, 56, 326-330 (1983) and "Kinetics of Nucleophilic Substitution Reactions of 2-Chloroquinoxaline with Aniline, Piperidine and Triethylamine in Pure Alkanols," *Gazetta Chimica Italiana*, 115 (12, Pt. B), 659-661. Thereafter, the second aryl group is coupled to Compound D to obtain a substituted aryl,aryl'-quinoxaline. Suitable reactions conditions include those discussed above for Scheme 1.



Compound D

Scheme 6

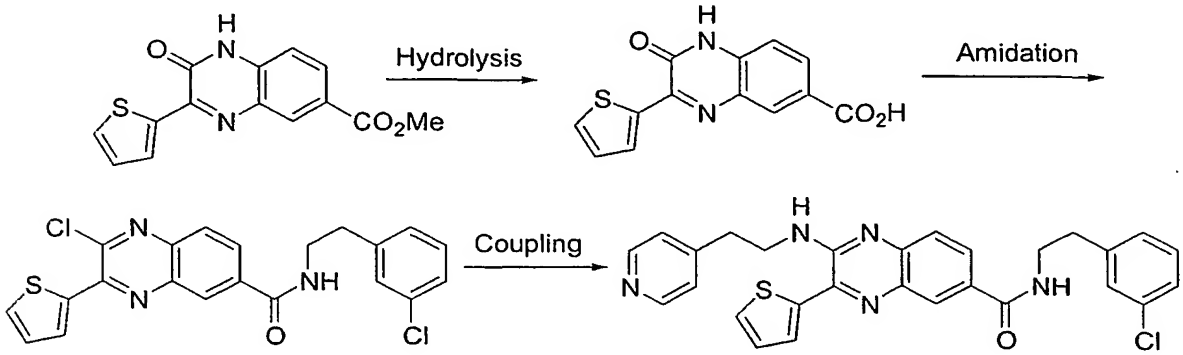
As discussed above, R_5 may represent a functional moiety that may be further functionalized by reduction, oxidation, alkylation, esterification, amidification, substitution, etc. Schemes 7 and 8 illustrate two methods wherein R_5 is further functionalized. One of ordinary skill in the art readily understands that these two methods merely are exemplary of a variety of methods, such as those described by "Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures," *J. Org. Chem.*, 61, 3849-3862 (1996). In Scheme 7, a nitro functional group is reduced to form an amine which is further functionalized by allowing the amine to react with an acyl chloride to form an amide.



Scheme 7

Alternatively, R_5 may be functionalized prior to the coupling reaction. For example, amidation may occur by the hydrolysis of an ester followed by amide formation. As illustrated in Scheme 8, an alkyl ester is hydrolyzed, and subsequently allowed to react with an amine to form an amide. Such functionalization procedures are commonly

known to one of ordinary skill in the art, for example in Li, *et al.*, "Highly efficient synthesis of peptides by rational utilization of novel coupling reagents," Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, Peop. Rep. China, *Chinese Journal of Chemistry*, 18(4), 456-466 (2000). Thereafter, the coupling step may be performed using an aralkyl amine in an inert organic solvent, such as DMF.



Scheme 8

The pharmaceutical compositions of the invention comprise compounds of Formula I or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof as an active ingredient, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients known to those skilled in the art. Preferred pharmaceutical compositions comprise at least one compound of Formula II, III, IIA, or IIIA.

Another embodiment of the invention encompasses pharmaceutical compositions, which include at least one compound of Formula I, II, III, IIA, or IIIA or a pharmaceutically acceptable salt, hydrate or pro-drug thereof, in combination with a pharmaceutically acceptable carrier.

Compositions of the invention are suitable for oral, mucosal (*e.g.*, nasal, vaginal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), sublingual, transdermal, or buccal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the part of pharmacy. Dosage forms include tablets, caplets, troches, lozenges, dispersions, suspensions, suppositories, solutions, capsules, soft elastic gelatin capsules, patches, and the like. Preferred dosage forms are those suitable for oral administration.

The compositions of the present invention may be employed in solid or liquid form including for example, powder or crystalline form, in solution or in suspension. The

choice of carrier and the content of active compound in the carrier are generally determined in accordance with the solubility and chemical properties of the desired product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. Thus, the carrier employed may be, for example, either a solid or liquid.

One method of administering a solid dosage form is to form solid compositions for rectal administration, which include suppositories formulated in accordance with known methods and containing at least one compound of the present invention. Examples of solid carriers include lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like.

Examples of liquid carriers include syrup, peanut oil, olive oil, water and the like. For parenteral administration, emulsions, suspensions or solutions of the compounds according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. Injectable forms must be fluid to the extent they can be easily syringed, and proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of the injectable compositions can be brought about by use of agents delaying absorption, for example, aluminum monostearate and gelatin.

The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. The aqueous solutions, also including solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation, microfiltration, and/or by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

Examples of injectable dosage forms include sterile injectable liquids, *e.g.*, solutions, emulsions and suspensions. Sterile injectable solutions are prepared by

incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation may include vacuum drying and a freeze-dry technique that yields a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

Examples of injectable solids include powders that are reconstituted, dissolved, or suspended in a liquid prior to injection. In injectable compositions, the carrier typically includes sterile water, saline or another injectable liquid, *e.g.*, peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included within the compositions of the present invention.

For oral administration, the active compound may be administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet, or may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Examples of oral solid dosage forms include tablets, capsules, troches, lozenges and the like. Examples of oral liquid dosage forms include solutions, suspensions, syrups, emulsions, soft gelatin capsules and the like. Carriers for oral use (solid or liquid) may include time delay materials known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax. To prepare a capsule, it may be advantageous to use lactose and liquid carrier, such as high molecular weight polyethylene glycols.

Topical administration, in the form of gels (water or alcohol based), creams or ointments, for example, containing compounds of the invention may be used. Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders. Such topical formulations can be used for example, to treat ocular diseases as well as inflammatory diseases such as rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reactions and the like.

Compounds of the invention may be also incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through transdermal barrier.

For administration by inhalation, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Compositions according to the invention may also be formulated in a manner that resists rapid clearance from the vascular (arterial or venous) wall by convection and/or diffusion, thereby increasing the residence time of the viral particles at the desired site of action. A periadventitial depot comprising a compound according to the invention may be used for sustained release. One such useful depot for administering a compound according to the invention may be a copolymer matrix, such as ethylene-vinyl acetate, or a polyvinyl alcohol gel surrounded by a Silastic shell. Alternatively, a compound according to the invention may be delivered locally from a silicone polymer implanted in the adventitia.

An alternative approach for minimizing washout of a compound according to the invention during percutaneous, transvascular delivery comprises the use of nondiffusible, drug-eluting microparticles. The microparticles may be included a variety of synthetic polymers, such as polylactide for example, or natural substances, including proteins or polysaccharides. Such microparticles enable strategic manipulation of variables including total dose of drug and kinetics of its release. Microparticles can be injected efficiently into the arterial or venous wall through a porous balloon catheter or a balloon over stent, and are retained in the vascular wall and the periadventitial tissue for at least about two weeks. Formulations and methodologies for local, intravascular site-specific delivery of therapeutic agents are discussed in Reissen et al. (*J. Am. Coll. Cardiol.* 23: 1234-1244 (1994)).

A composition according to the invention may also comprise a hydrogel which is prepared from any biocompatible or non-cytotoxic (homo or hetero) polymer, such as a hydrophilic polyacrylic acid polymer that can act as a drug absorbing sponge. Such polymers have been described, for example, in application WO93/08845. Certain of them, such as, in particular, those obtained from ethylene and/or propylene oxide are commercially available.

Another embodiment of the invention provides for a compound according to the invention to be administered by means of perfusion balloons. These perfusion balloons, which make it possible to maintain a blood flow and thus to decrease the risks of ischaemia of the myocardium, on inflation of the balloon, also enable the compound to be delivered locally at normal pressure for a relatively long time, more than twenty minutes, which may be necessary for its optimal action.

Alternatively, a channeled balloon catheter (such as "channeled balloon angioplasty catheter", Mansfield Medical, Boston Scientific Corp., Watertown, Mass.) may be used. This catheter includes a conventional balloon covered with a layer of 24 perforated channels that are perfused via an independent lumen through an additional infusion orifice. Various types of balloon catheters, such as double balloon, porous balloon, microporous balloon, channel balloon, balloon over stent and hydrogel catheters, all of which may be used to practice the invention, are disclosed in Reissen *et al.* (1994).

Another aspect of the present invention relates to a pharmaceutical composition including a compound according to the invention and poloxamer, such as Poloxamer 407, which is a non-toxic, biocompatible polyol, commercially available (*e.g.*, from BASF, Parsippany, N.J.). A poloxamer impregnated with a compound according to the invention may be deposited for example, directly on the surface of the tissue to be treated, for example during a surgical intervention. Poloxamer possesses essentially the same advantages as hydrogel while having a lower viscosity. The use of a channel balloon catheter with a poloxamer impregnated with a compound according to the invention may be advantageous in that it may keep the balloon inflated for a longer period of time, while retaining the properties of facilitated sliding, and of site-specificity of the poloxamer.

The composition may also be administered to a patient via a stent device. In this embodiment, the composition is a polymeric material in which the compound of the invention is incorporated, which composition is applied to at least one surface of the stent device.

Polymeric materials suitable for incorporating the compound of the invention include polymers having relatively low processing temperatures such as polycaprolactone, poly(ethylene-co-vinyl acetate) or poly(vinyl acetate or silicone gum rubber and polymers having similar relatively low processing temperatures. Other suitable polymers include non-degradable polymers capable of carrying and delivering therapeutic drugs such as latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers (SEBS) and biodegradable, bioabsorbable polymers capable of

carrying and delivering therapeutic drugs, such as poly-DL-lactic acid (DL-PLA), and poly-L-lactic acid (L-PLA), polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes.

In addition to the active compound and the pharmaceutically acceptable carrier, the compositions of the present invention optionally contain one or more excipients that are conventional in the art. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silica gels combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets, troches, pills, capsules and the like.

Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. When aqueous suspensions are used they may contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyols such as polyethylene glycol, propylene glycol and glycerol, and chloroform or mixtures thereof may also be used. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The percentage of active ingredient in the compositions of the invention may be varied. Several unit dosage forms may be administered at about the same time. A suitable dose employed may be determined by a physician or qualified medical professional, and depends upon various factors including the desired therapeutic effect, the nature of the illness being treated, the route of administration, the duration of the treatment, and the condition of the patient, such as age, weight, general state of health and other characteristics, which can influence the efficacy of the compound according to the invention. In adults, doses are generally from about 0.001 to about 100 mg/kg body weight and preferably, about 0.01 to about 100 mg/kg body weight per day.

The compounds and compositions according to the invention may be administered as frequently as necessary as determined by a skilled practitioner in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. For other patients, it may be necessary to prescribe not more than one or two doses per day.

The compounds of the present invention may also be formulated for use in conjunction with other therapeutically active compounds or in connection with the application of therapeutic techniques to address pharmacological conditions, which may be ameliorated through the application of a compound according to the present invention.

One embodiment of the invention encompasses method of treating cancer using the compounds of the invention. The disclosed compounds can be used to treat subjects with cancer, including multi-drug resistant cancers. A cancer is resistant to a drug when it resumes a normal rate of tumor growth while undergoing treatment with the drug after the tumor had initially responded to the drug. The term "multi-drug resistant cancer" refers to cancer that is resistant to two or more drugs, typically five or more.

The disclosed compounds can be co-administered with other anticancer agents such as Taxol, Vincristine, Adriamycin, Etoposide, Doxorubicin, Dactinomycin, Mitomycin C, Bleomycin, Vinblastine, Cisplatin, Erbitux, Avastin, Irressa, and the like. Additionally, the disclosed compounds can be co-administered with bioactive anticancer agents such as kinase inhibitors, kinase receptors, antigenesis inhibitors, cell cycle inhibitors, cytotoxic targeting agents, signal transduction pathway inhibitors, and the like. The method can also be carried in combination with other cancer treatments such as surgery, radiation, and the like.

Moreover, the compounds of Formula I may be used for *in vivo* and *in vitro* investigative, diagnostic, or prophylactic methods, which are well known in the art.

The methods of the present invention encompass administration of a therapeutically effective amount of at least one compound of Formula I to a subject in need of such treatment. As used herein, the term "administering" means delivering the compounds of the present invention to a subject by any method that may achieve the result sought. The method may be, for example, orally, parenterally (intravenously or intramuscularly), topically, transdermally, or by inhalation. The term "subject" as used herein is intended to include, but is not limited to, humans, laboratory animals, domestic pets and farm animals. The term "therapeutically effective amount" as used herein with respect to the treatment or prevention of cancer encompasses an amount of compound of the present invention that reduces the rate of PKB phosphorilation of a target as compared to the rate in the absence of a compound of the invention, preferably the rate is about 20% to about 100%.

Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art.

Similarly, amounts sufficient to treat or prevent such disorders, but insufficient to cause adverse effects associated with compounds of Formula I, are also encompassed by dosage amounts and dose frequency schedules.

The compounds of the invention were tested using a variety of assays. Assays used include PKBα *in vitro* kinase assay, cell-based GSK-3β phosphorylation assay, and generation of MCF-7 cells expressing myristoylated PKBα. The following tables summarized the assay data. The assays are discussed briefly, however, the experimental section discusses the assays in more detail.

Typically, the PKBα *in vitro* kinase assay to determine PKBα enzyme activity was performed for 45 minutes at room temperature in kinase buffer (2 μM ATP, 0.71 μCi ^{33}P-ATP, 4% inhibitor in DMSO (v/v), 25 mM Tris, 2 mM DTT and 10 mM $MgCl_2$) containing various concentrations of the compounds of the invention. Each reaction contained 50 ng of recombinant PKBα kinase domain and 250 ng of biotinylated target peptide (derived from GSK-3) bound to a streptavidin-coated 96-well plate. The incorporated radioactivity was quantified by liquid scintillation.

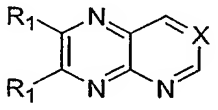
The cell-based GSK-3β phosphorylation assay was conducted as follows. Serum-starved MCF-7 breast carcinoma cells in 24-well tissue culture plates were treated for 2 hours with the compounds of the invention before the addition of 10 nM IGF-1 for 30 minutes. Thereafter, the cells were lysed in lysis buffer (20 mM Tris, pH 7.4, 137 mM NaCl, 1% Triton X-100, 2 mM EDTA and 10% glycerol supplemented with 1x protease inhibitor cocktail, Sigma phosphatase inhibitor cocktails I and II, 0.5 U/μl DNase I and 5 mM $MgCl_2$) and cell extract was added to 96-well plates coated with mouse anti-GSK-3β capture antibody (BD Transduction Labs #610202). After an overnight incubation, the plate was blocked with 3% BSA and incubated with 50 μl/well of cell extract for 5 hrs at room temperature. Bound phospho-GSK-3β was detected with rabbit anti-phospho-GSK-3α/β antibody (Cell Signaling Technology #9331) and an HRP-conjugated secondary antibody. Signal was detected using a TR717 luminometer (PE Applied Biosystems) and a chemiluminescent substrate (Pierce #37070).

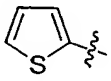
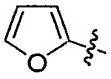
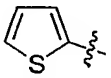
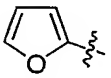
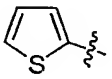
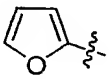
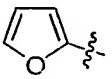
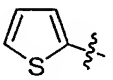
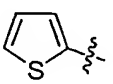
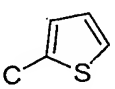
The generation of MCF-7 cells expressing myristoylated PKBα was performed as follows. MCF-7 cells were electroporated with 50 μg myr-Akt1 cDNA in pUSEamp(+) (Upstate #21-151) and selected with 800 μg/ml G418. Resistant clones were picked, expanded and maintained in media containing 500 μg/ml G418.

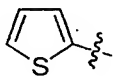
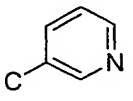
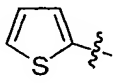
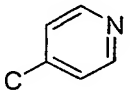
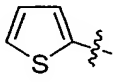
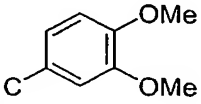
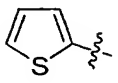
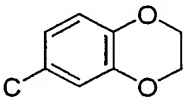
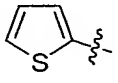
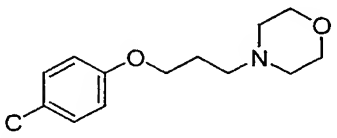
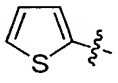
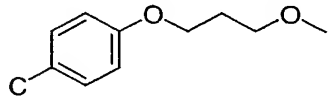
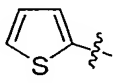
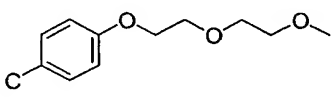
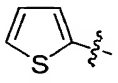
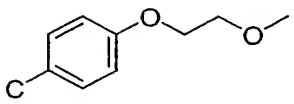
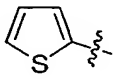
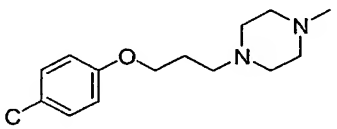
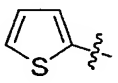
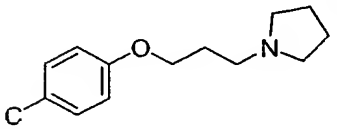
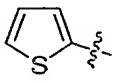
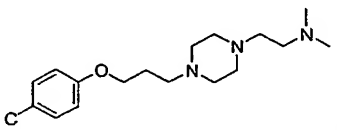
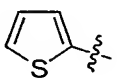
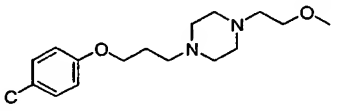
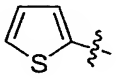
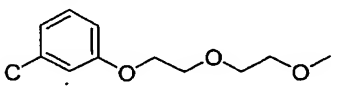
The *in vitro* kinase assay for PKB isoforms was performed as follows. PKBα, PKBβ, and PKBγ proteins (Upstate) were activated according to manufacturer's instructions. 400 pg of the enzyme was added to kinase reaction buffer (2 μM ATP, 10 mM $MgCl_2$, 8 mM MOPS, pH 7.0 and 0.2 μM EDTA) and 250 ng biotinylated target peptide bound to a streptavidin-coated 96-well plate containing various concentrations of the compounds of the invention. Phosphorylation of the target peptide was detected as described above.

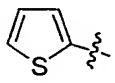
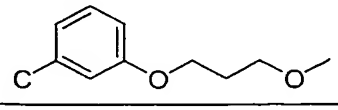
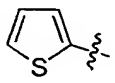
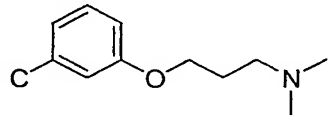
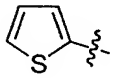
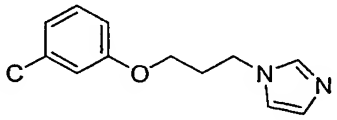
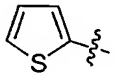
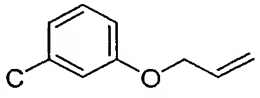
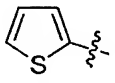
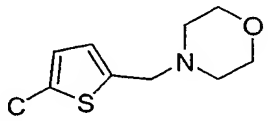
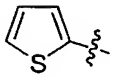
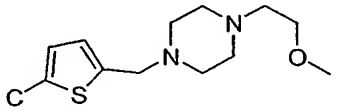
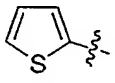
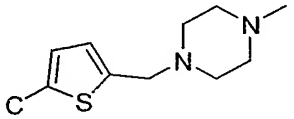
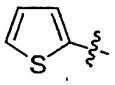
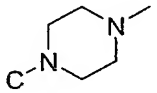
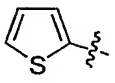
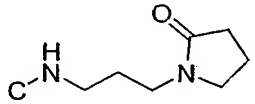
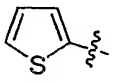
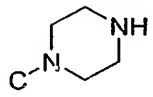
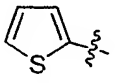
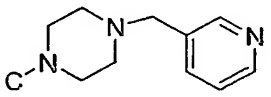
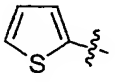
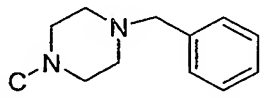
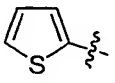
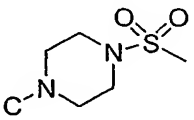
The following tables summarize the test data for various compounds of the invention. Table 1 summarizes the assay data for pteridine and pyrido[2,3-b]pyrazine compounds of the invention.

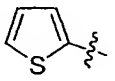
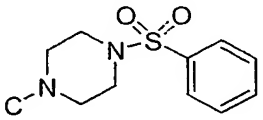
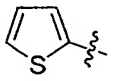
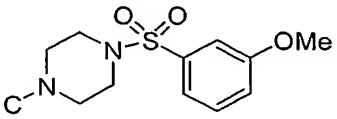
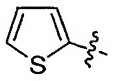
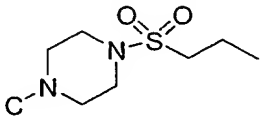
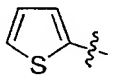
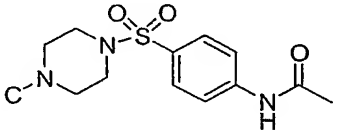
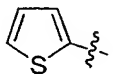
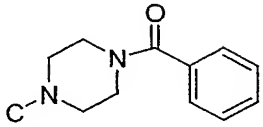
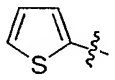
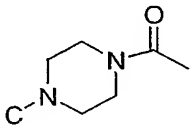
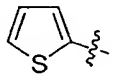
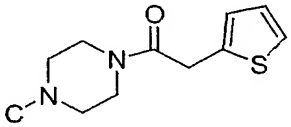
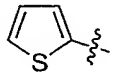
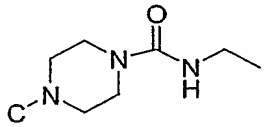
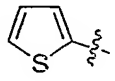
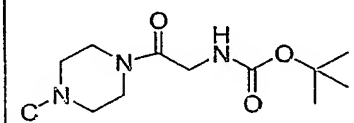
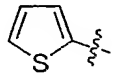
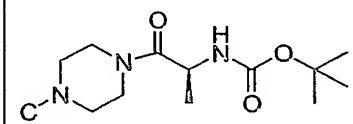
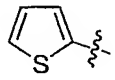
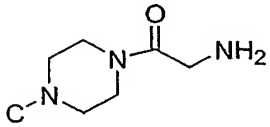
Table 1. Assay data for Compounds of Formula:

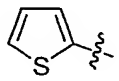
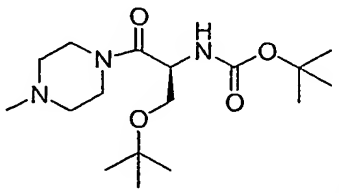


Comp. No.	R_1	X	Anticancer assay (act.)[a]		
			No. 1[b]	No. 2[c]	No. 3[d]
1		N	46	65.6	
1b		N	42	9.8	
2		C-H	71	29.6	
3		C-H	30	10.3	
4		C-Br	79	1.7	0.3
5		C-Br	76	1.6	nd
5b		C-Cl	62	3.5	
23		C-CN	74	1.5	
43			88	nd	0.1

44			63	0.8	nd
45			64		
46			57		
47			56		
49			82	0.3	0.5
50			93		
51			30	nd	21.9
52			76	nd	2.3
54			38		
55			70		
56			37		
57			49		
59			34		

60			37	nd	2.2
63			82[c]	nd	8.4
64			54		
65			22		
69			25	nd	1.6
70			38	nd	0.2
71			84		
73			80	1.5	
74			34	25	
75			45	4.5	
76			37	8.6	27.0
77			49	0.9	3.0
78			91	2.7	nd

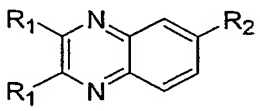
79			43	8.8	
80			67	1.2	
81			68	2.4	2.0
82			41	28.0	
83			91	2.3	nd
84			63	13.0	
85			77	1.2	1.6
86			43	16.0	0.4
87			79	1.9	
88			78	1.7	
89			54	24.0	

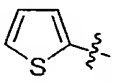
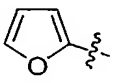
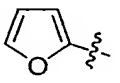
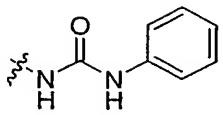
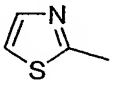
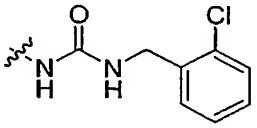
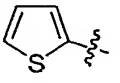
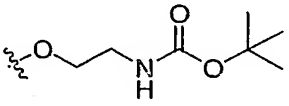
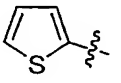
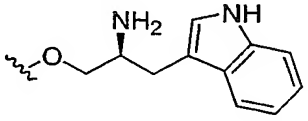
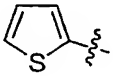
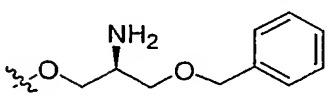
90			80	0.8	

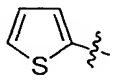
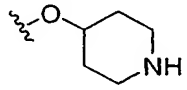
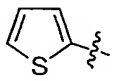
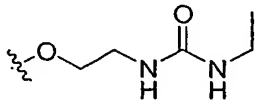
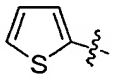
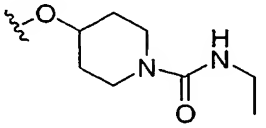
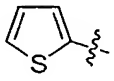
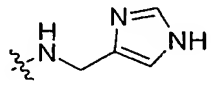
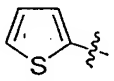
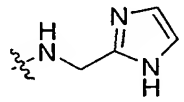
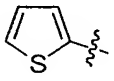
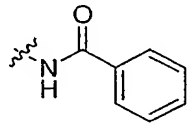
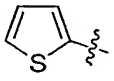
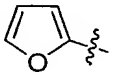
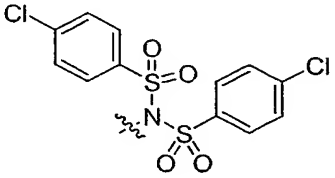
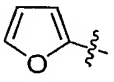
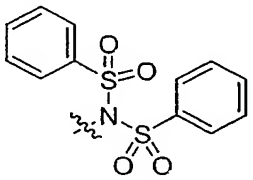
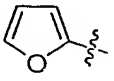
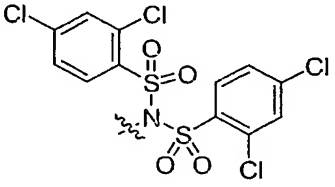
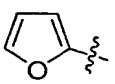
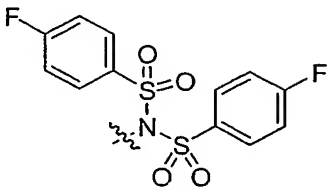
[a] Wherein assay is measured by activity.
[b] Assay No. 1 is the *in vitro* PKB Activity Assay measured as % inhibition at 10 μM compound concentration unless specified otherwise.
[c] Assay No. 2 is the *in vitro* PKB Activity Assay measured as IC_{50} (μM).
[d] Assay No. 3 is the PKB Cell Based Assay measured as IC_{50} (μM).
[e] At 33 μM compound concentration.

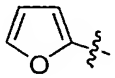
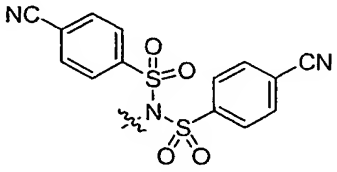
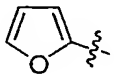
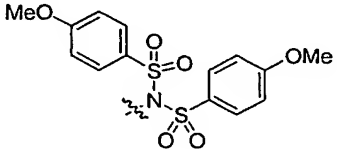
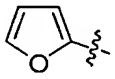
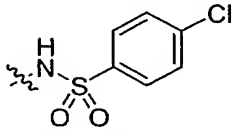
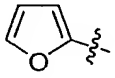
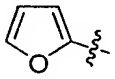
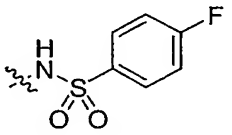
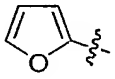
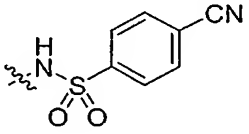
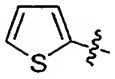
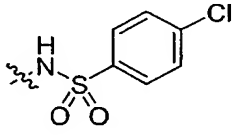
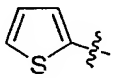
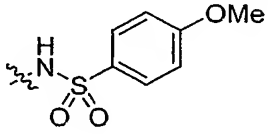
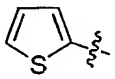
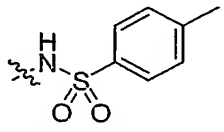
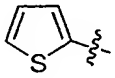
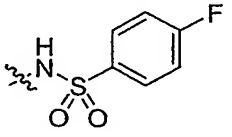
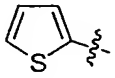
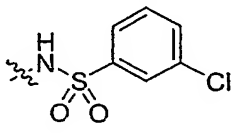
Table 2 summarizes the assay data for quinoxaline compounds of the invention.

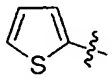
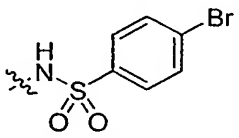
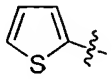
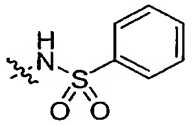
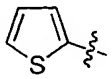
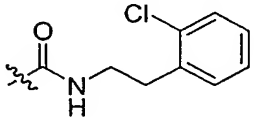
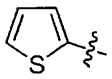
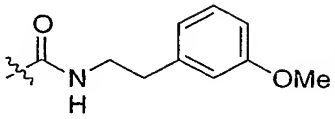
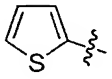
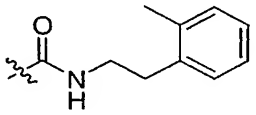
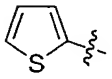
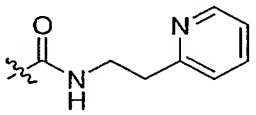
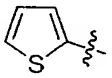
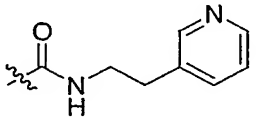
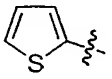
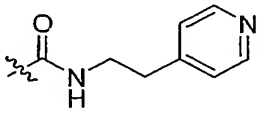
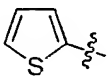
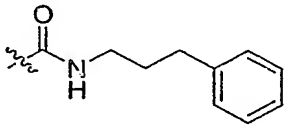
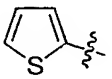
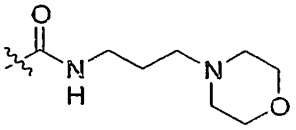
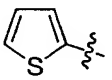
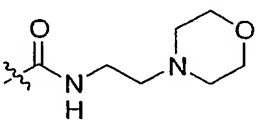
Table 2. Assay data for Compounds of Formula:



Comp. No.	R_1	R_2	Anticancer assay (act.)[a]		
			No. 1[b]	No. 2[c]	No. 3[d]
8		Me	90	3.1	
9		Me	61	2.1	
21			94	1.4	
22			64	5.8	
31			40		
33			56		
34			49		

35			46		
36			45		
37			34		
38			54[e]	0.5	
39			53[e]	0.8	
40			81[e]	0.7	34
93		OMe	59	45.0	0.4
94			87[e]	3.5	
95			78[e]	17.0	
96			73		
97			52		

98			58		
99			58		
100			93	0.6	1.2
101			91	0.6	
102			85	0.6	
103			85	0.9	
104			32		
105			29		
106			30		
107			33		
108			35		

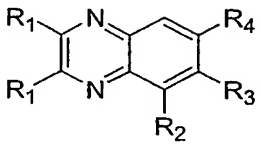
109			34		
110			30		
148			30[e]	0.4	8.2
140			45	0.8	
141			60[e]	0.5	
142			60[e]	1.9	
143			35	19.7	36.6
144			71	3.8	
145			25		
146			33[e]	17.4	
147			29	5.9	

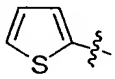
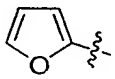
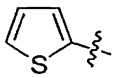
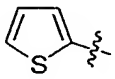
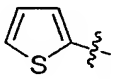
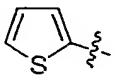
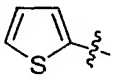
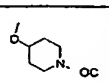
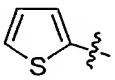
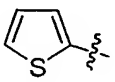
[a] Wherein assay is measured by activity.

[b] Assay No. 1 is the *in vitro* PKB Activity Assay measured as % inhibition at 10 μM compound concentration unless specified otherwise.
[c] Assay No. 2 is the *in vitro* PKB Activity Assay measured as IC_{50} (μM).
[d] Assay No. 3 is the PKB Cell Based Assay measured as IC_{50} (μM).
[e] At 25 μM concentration.

Table 3 and 4 summarize assay data for quinoxaline compounds of the invention.

Table 3. Assay data for Compounds of Formula:

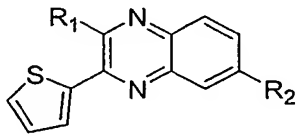


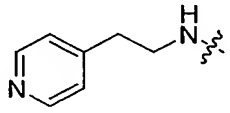
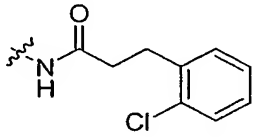
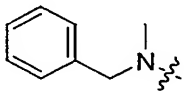
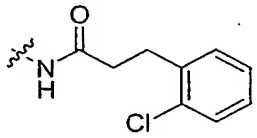
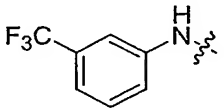
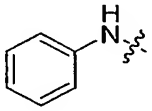
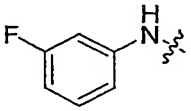
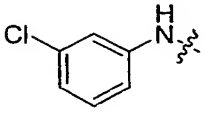
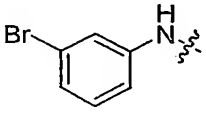
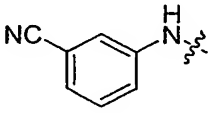
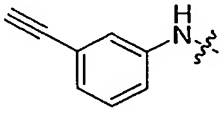
Comp. No.	R_1	R_2	R_3	R_4	Anticancer assay (act.)[a]		
					No. 1[b]	No. 2[c]	No. 3[d]
6		Me	H	H	90	25.4	0.4
7		Me	H	H	71	1.8	
12		H	Me	Me	59	4.9	
13		H	Cl	Cl	77	0.7	79
14		H	F	F	70	3.1	2.8
15		F	F	H	70	7.1	
24			H	H	31		
91		H	F	Cl	31	59	
92		H	Me	Cl	58	82	

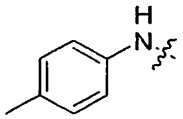
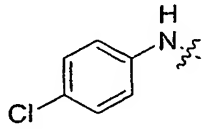
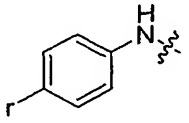
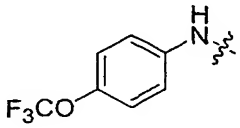
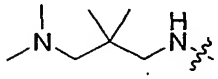
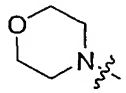
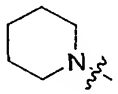
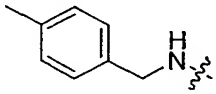
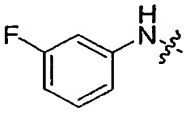
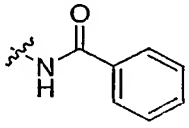
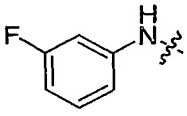
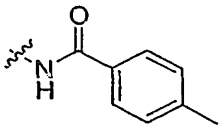
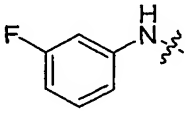
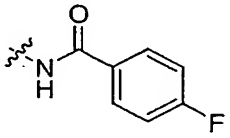
[a] Wherein assay is measured by activity.
[b] Assay No. 1 is the *in vitro* PKB Activity Assay measured as % inhibition at 10 μM compound concentration unless specified otherwise.
[c] Assay No. 2 is the *in vitro* PKB Activity Assay measured as IC_{50} (μM).

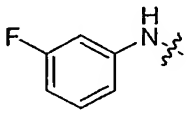
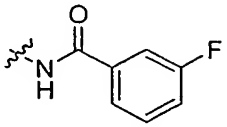
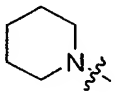
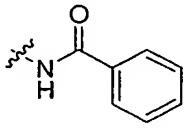
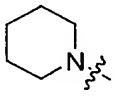
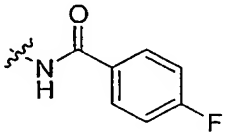
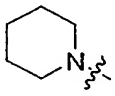
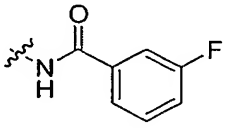
[d] Assay No. 3 is the PKB Cell Based Assay measured as IC_{50} (μM).

Table 4. Assay data for Compounds of Formula:



Comp. No.	R_1	R_2	Anticancer assay (act.)[a]		
			No. 1[b]	No. 2[c]	No. 3[d]
27				2.6	
28				2.3	
112		H	60	2.5	.....
113		H	87	15.0	13
114		H	83	4.0	
115		H	85	4.0	
116		H	84	6.0	
117		H	47		
118		H	67		3.1

119		H	59	4.4	
120		H	63	4.4	
121		H	65	3.6	
122		H	66		
123		H	28		
124		H	52		
125		H	75	5.1	
126		H	47		
127		H	66		
132			52		0.1
133			40		
134			36		4.5

135			34		
136			39		0.3
137			30		
138			29		

[a] Wherein assay is measured by activity.
[b] Assay No. 1 is the *in vitro* PKB Activity Assay measured as % inhibition at 10 μM compound concentration unless specified otherwise.
[c] Assay No. 2 is the *in vitro* PKB Activity Assay measured as IC_{50} (μM).
[d] Assay No. 3 is the PKB Cell Based Assay measured as IC_{50} (μM).

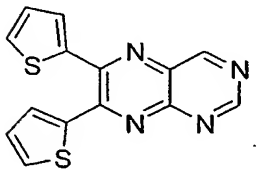
The above examples are intended to be illustrative only. In particular, the invention is not intended to be limited to the methods, protocols, conditions and the like specifically recited herein, insofar as those skilled in the art would be able to substitute other conditions, methods, amounts, materials, etc. based on the present disclosure to arrive at compounds within the scope of this disclosure. While the present invention is described with respect to particular examples and preferred embodiments, the present invention is not limited to these examples and embodiments. In particular, the compounds of the present invention are not limited to the exemplary species' recited herein. Moreover, the methods of the present invention are not limited to treating only the exemplified diseases and conditions, but rather any disease or condition that may be treated by regulation of kinases. Additionally, the methods of synthesis of the present invention are not limited to the methods exemplified in the example. The methods of the present invention include methods of making any of the compounds set forth in the present invention that those skilled would be able to make in view of the present disclosure, and are not limited to the exemplified method. For example, methods encompassed by the present invention may involve the use of a different starting material depending on the desired final compound, different amounts of various ingredients, or

substitution of different ingredients such as other reactants or catalysts that would be suitable depending on the starting material and result to be achieved.

The invention is further defined by reference to the following examples, describing in detail the preparation of the compound and the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

Examples

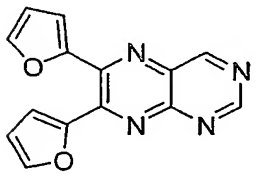
Example 1: Compound 1



6,7-Dithiophen-2-yl-pteridine: In a pressure tube 4,5-diaminopyrimidine (25 mg, 0.23 mmol) and 2,2'-thenil (50 mg, 0.23 mmol) were suspended in 3 ml ethanol. After heating overnight at 100°C the cooled reaction mixture was concentrated and purified by preparative TLC using 5% methanol in dichloromethane as an eluant. (13 mg; 19%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 9.41 (s, 1H), 7.57 (dd, J = 5.1, 0.9 Hz, 1H), 7.54 (dd, J = 5.4, 1.2 Hz, 1H), 7.44 (dd, J = 3.9, 0.9 Hz, 1H), 7.42 (dd, J = 3.6, 0.9 Hz, 1H), 7.04 (dd, J = 5.1, 4.8 Hz, 1H), 6.98 (dd, J = 5.1, 4.8 Hz, 1H). ESI MS: 297 (M+1). The assay data yielded PI@10μM = 45.7 and an IC_{50} = 65.6μM.

The following compounds were prepared in analogous manner:

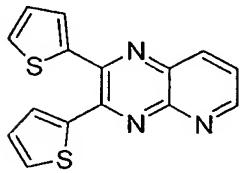
Example 1b: Compound 1b



6,7-Difuran-2-yl-pteridine: From 4,5-diaminopyrimidine and 2,2'-furil(49%). Eluant was 5% methanol in dichloromethane (30 mg, 49%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 9.43 (s, 1H), 7.60 (dd, J = 1.8, 0.9 Hz, 1H), 7.59 (dd, J = 1.8, 0.9 Hz, 1H),

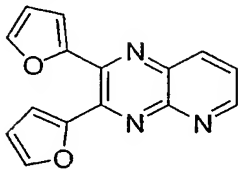
7.11 (dd, J = 3.6, 0.6Hz, 1H), 6.85 (dd, J = 3.6, 0.6Hz, 1H), 6.57 (m, 2H). ESI MS: 265 (M+1). The assay data yielded: PI@25μM = 41.5 and an IC_{50} = 9.84 μM.

Example 2: Compound 2



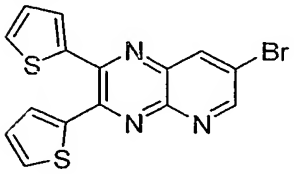
2,3-Dithiophen-2-yl-pyridino[2,3-*b*]pyrazine. From 2,3-diaminopyridine and 2,2'-thenil. Elution solvent was 10% ethyl acetate in dichloromethane (43 mg, 68%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.05 (dd, J = 4.2, 1.8 Hz, 1H), 8.36 (dd, J = 8.4, 1.8 Hz, 1H) 7.61 (dd, J = 8.4, 4.2 Hz, 1H), 7.50 (m, 2H), 7.35 (m, 2H), 7.04 (dd, J = 5.1, 5.1 Hz, 1H), 6.98 (dd, J = 5.1, 5.1 Hz, 1H). ESI MS: 296 (M+1.) The assay data yielded PI@ 10 μM = 70.9 and an IC_{50} = 29.6 μM.

Example 3: Compound 3



2,3-Difuran-2-yl-pyridino[2,3-*b*]pyrazine. From 2,3-diaminopyridine and 2,2'-furil. Elution solvent was 10% ethyl acetate in dichloromethane (46 mg, 76%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.25 (dd, J = 4.2, 1.8 Hz, 1H), 8.60 (dd, J = 8.4, 2.1 Hz, 1H), 7.80 (m, 2H), 7.74 (m, 1H), 7.21 (d, J = 3.3 Hz, 1H), 6.87 (d, J = 3.6 Hz, 1H), 6.73 (m, 2H). ESI MS: 264 (M+1). The assay data yielded PI@10μM = 29.7 and an IC_{50} = 10.3 μM.

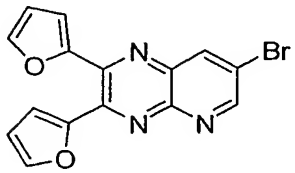
Example 4: Compound 4



7-Bromo-2,3-dithiophen-2-yl-pyridino[2,3-*b*]pyrazine. From 2,3-diamino-5-bromopyridine and 2,2'-thenil. Elution solvent was 10% ethyl acetate in dichloromethane (58 mg, 67%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.27 (d, J = 2.1 Hz, 1H), 8.76 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 5.1, 2H), 7.62 (d, J = 3.6, 2H), 7.28 (dd, J = 5.1, 5.1 Hz, 1H), 7.24

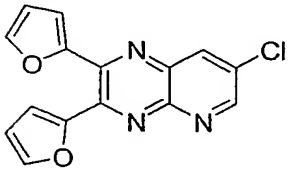
(dd, J = 4.8, 4.8 Hz, 1H). ESI MS: 375 (M+1). The assay data yielded PI@10μM = 100% and an IC_{50} = 0.3 μM.

Example 5: Compound 5



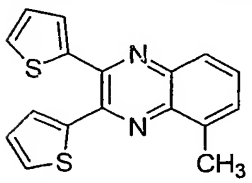
7-Bromo-2,3-difuran-2-yl-pyridino[2,3-*b*]pyrazine. From 2,3-diamino-5-bromopyridine and 2,2'-furil. Elution solvent was 10% ethyl acetate in dichloromethane (47 mg, 60%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.95 (d, J = 2.4 Hz, 1H), 8.47 (d, J = 2.4 Hz, 1H), 7.49 (dt, J = 12.9, 0.9 Hz, 2H), 6.94 (d, J = 3.6 Hz, 1H), 6.64 (d, J = 3.6 Hz, 1H), 6.46 (m, 2H). ESI MS: 343 (M+1). The assay data yielded PI@10μM = 76.5% and an IC_{50} = 1.56 μM.

Example 5b: Compound 5b



7-Chloro-2,3-difuran-2-yl-pyridino[2,3-*b*]pyrazine. From 2,3-diamino-5-chloropyridine and 2,2'-furil. Product precipitated from the reaction mixture (989 mg, 95%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.01 (d, J = 2.1Hz, 1H), 8.42 (d, J = 2.1Hz), 7.65 (s, 1H), 7.61 (s, 1H), 7.07 (d, J = 3.3 Hz, 1H), 6.78 (d, J = 3.3 Hz, 1H), 6.60 (m, 2H). ESI MS: 298 (M+1). The assay data yielded PI@25μM = 62.2% and an IC_{50} = 3.47μM.

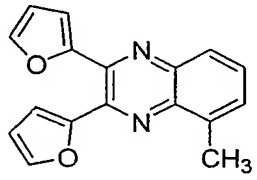
Example 6: Compound 6



5-Methyl-2,3-dithiophen-2-yl-quinoxaline. From 2,3-diaminotoluene and 2,2'-thenil. The product crystallized from the crude reaction mixture and was isolated by filtration. No additional purification was necessary (54 mg, 76%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.1, 1.2 Hz, 1H), 7.56 - 7.39 (m, 4H), 7.26 (dd, J = 3.6, 0.9 Hz,

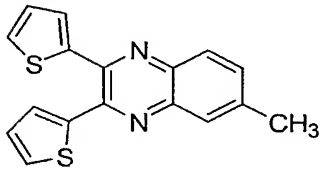
1H), 7.14 (dd, J = 3.9, 1.2 Hz, 1H), 7.00 (dd, J = 5.1, 5.1 Hz, 1H), 6.94 (dd, J = 5.1, 5.1 Hz, 1H) 2.75 (s, 3H). ESI MS: 309 (M+1). The assay data yielded PI@ 10 μM = 90.2% and an IC_{50} = 2.54 μM.

Example 7: Compound 7



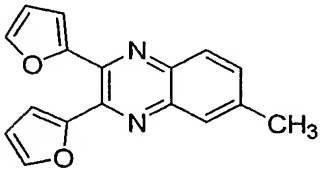
5-Methyl-2,3-difuran-2-yl-quinoxaline. From 2,3-diaminotoluene and 2,2'-furil. The product crystallized from the crude reaction mixture and was isolated by filtration. No additional purification was necessary (27 mg, 43%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.1 Hz, 1H) 7.76 - 7.66 (m, 4H), 6.91 (dd, J = 3.3, 0.9 Hz, 1H), 6.69 - 6.63 (m, 3H), 2.92 (s, 3H). ESI MS: 277 (M+1). The assay data yielded PI@ 10 μM = 70.6% and an IC_{50} = 1.83 μM.

Example 8: Compound 8



6-Methyl-2,3-dithiophen-2-yl-quinoxaline. From 3,4-diaminotoluene and 2,2'-thenil. The product crystallized from the crude reaction mixture and was isolated by filtration. No additional purification was necessary (54 mg, 67%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.55 (dd, J = 8.4, 0.9 Hz, 1H), 7.48 (d, J = 4.5, 2H), 7.22 (m, 2H), 7.03 (m, 2H) 2.58 (s, 3H). ESI MS: 309 (M+1). The assay data yielded PI@ 10 μM = 90.5% and an IC_{50} = 1.34 μM.

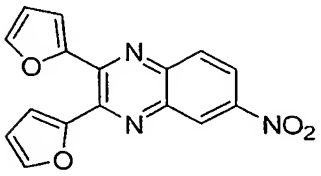
Example 9: Compound 9



6-Methyl-2,3-difuran-2-yl-quinoxaline. From 3,4-diaminotoluene and 2,2'-furil. Elution solvent was 25% ethyl acetate in hexane (50 mg, 79%). ^{1}H-NMR (300 MHz,

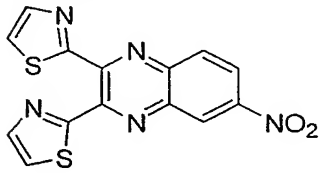
$CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.54 - 7.48 (m, 3H), 6.54 (d, J = 3.3 Hz, 2H), 6.48 - 6.46 (m, 2H), 2.51 (s, 3H). ESI MS: 277 (M+1). The assay data yielded PI@ 10 μM = 61.2% and an IC_{50} = 2.11 μM.

Example 10



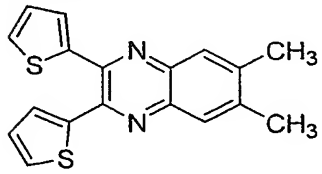
6-Nitro-2,3-difuran-2-yl-quinoxaline. From 4-nitro-benzymaticene-1,2-diamine and 2,2'-furil. The product crystallized from the crude reaction mixture and was isolated by filtration. No additional purification was necessary (9.45 g, 98%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 2.7 Hz, 1H), 8.27 (dd, J = 9.0, 2.4 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.45 (dd, J = 5.4, 0.9 Hz, 2H), 6.63 (dd, J = 16.5, 3.6, 2H), 6.41 - 6.38 (m, 2H). ESI MS: 308 (M+1).

Example 11



6-Nitro-2,3-bis-thiazol-2-yl-quinoxaline. From 4-nitro-phenylene-1,2-diamine and 2,2'-thiazolil (prepared according to the procedure by Beyer and Hess, Chem. Ber., 1957, 90, 2435-2439). The product was recrystallized from ethanol (682 mg, 90%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.28 (d, J = 2.4 Hz, 1H), 8.79 (dd, J = 9.0, 2.4 Hz, 1H), 8.52 (d, J = 9.3 Hz, 1H), 8.1 (2d, J = 3.0 Hz, 2H), 7.81 (d, J = 3.0 Hz, 2H). ESI MS: 342 (M+1).

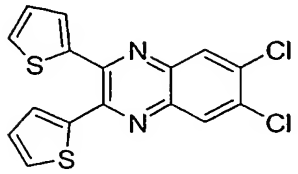
Example 12: Compound 12



6,7-Dimethyl-2,3-dithiophen-2-yl-quinoxaline. From 4,5-dimethyl phenylene-1,2-diamine and 2,2'-thenil. This product was isolated from the crude reaction mixture by re-crystallization in ethanol (57 mg, 74%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 2H), 7.73

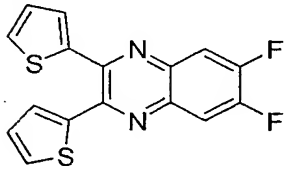
(dd, J = 5.1, 0.9 Hz, 2H), 7.10 (dd, J = 3.9, 0.9 Hz, 2H), 6.92 (dd, J = 5.1, 5.1 Hz, 2H), 2.39 (s, 6H). ESI MS: 323 (M+1). The assay data yielded PI@ 10 μM = 59.0% and an IC_{50} = 4.89 μM.

Example 13: Compound 13



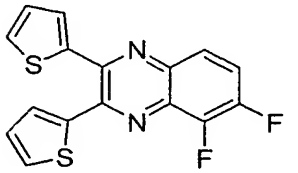
6,7-Dichloro-2,3-dithiophen-2-yl-quinoxaline. From 4,5-dichloro phenylene-1,2-diamine and 2,2'-thenil. This product was isolated from the crude reaction mixture by re-crystallization in ethanol (55 mg, 66%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.31 (dd, J = 5.1, 0.9 Hz, 2H), 7.07 (dd, 3.6, 0.9 Hz, 2H), 6.82 (dd, J = 5.1, 5.1 Hz, 2H). ESI MS: 362 (M+1, ^{35}Cl). The assay data yielded PI@ 10 μM = 76.8%, IC_{50} = 0.67 μM and a cell IC_{50} = 79 μM.

Example 14: Compound 14



6,7-Difluoro-2,3-dithiophen-2-yl-quinoxaline. From 4,5-difluoro phenylene-1,2-diamine and 2,2'-thenil. This product was isolated from the crude reaction mixture by re-crystallization in ethanol (53 mg, 70%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (t, J = 9.3 Hz, 2H), 7.42 (dd, J = 4.8, 0.9 Hz, 2H), 7.17 (3.3, 0.9 Hz, 2H), 6.95 (dd, J = 5.1, 5.1Hz, 2H). ESI MS: 331 (M+1). The assay data yielded PI@ 10 μM = 70.0%, IC_{50} = 3.12 μM and a cell IC_{50} = 2.79 μM.

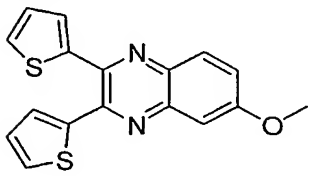
Example 15: Compound 15



5,6-Difluoro-2,3-dithiophen-2-yl-quinoxaline. From 3,4-difluoro phenylene-1,2-diamine and 2,2'-thenil. This product was isolated from the crude reaction mixture by re-

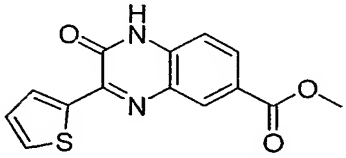
crystallization in ethanol (54 mg, 71%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (ddd, J = 9.3, 7.8, 2.1 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.30 (td, J = 3.9, 1.2 Hz, 2H), 7.04 (m, 2H). ESI MS: 331 (M+1). The assay data yielded PI@ 10 μM = 69.8%, and an IC_{50} = 7.13 μM.

Example 16



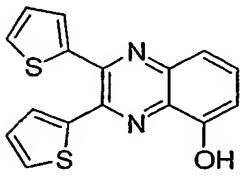
6-methoxy-2,3-dithiophen-2-yl-quinoxaline. From 4-methoxy-1,2-phenylenediamine di-hydrochloride and 2,2'thenil. The product crystallized from the crude reaction mixture and was isolated by filtration. No additional purification was necessary (4.07 g, 93%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 10.2 Hz, 1H), 7.40 (td, J = 4.2, 0.9 Hz, 2H), 7.32 - 7.28 (m, 2H), 7.13 (dt, J = 3.6, 1.2 Hz, 2H), 6.98 - 6.94 (m, 2H), 3.91 (s, 3H). ESI MS: 325 (M+1).

Example 17



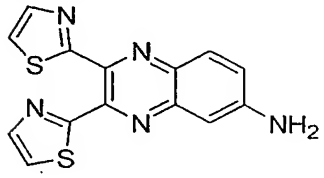
2-Oxo-3-thiophen-2-yl-1,2-dihydroquinoxaline-6-carboxylic acid methyl ester. From methyl 3,4-diaminobenzymaticoate and thiophene-2-glyoxylic acid ethyl ester. The product precipitated from the crude reaction mixture and was isolated by filtration as an inseparable mixture of regioisomers (1.05 g, 61%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.7 (s, 1H), 12.6 (s, 1H), 8.24 (dd, J = 3.9, 1.2 Hz, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 8.4, 1.8Hz, 1H), 7.70 - 7.61 (m, 5H), 7.18 (d, J = 8.4 Hz, 1H), 7.06 - 7.02 (m, 2H), 3.71 (s, 6H). ESI MS: 286 (M+1).

Example 18



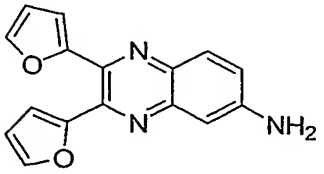
2,3-Dithiophen-2-yl-5-hydroxyquinoxaline. 3-hydroxy-1,2-phenylenediamine (100 mg, 0.45 mmol), 2,2'-thenil (56 mg, 0.45 mmol) and p-toluenesulfonic acid (9 mg, 0.045 mmol) were placed in a pressure tube and suspended in 1 ml of ethanol. The tube was sealed and heated to 100°C for 18 hours, after which, the crude mixture was partitioned between water and ethyl acetate. After washing the aqueous layer a second time with more ethyl acetate the combined layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to a brown solid which was used without further purification (144 mg, 100%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.71 (dd, J = 5.1, 1.2 Hz, 2H), 7.58 (t, J = 8.4 Hz, 1 H), 7.40 (dd, J = 8.4, 1.2 Hz, 1H), 7.28 (dd, J = 3.6, 1.2 Hz, 1H), 7.10 - 7.01 (m, 4 H). ESI MS: 311 (M+1).

Example 19



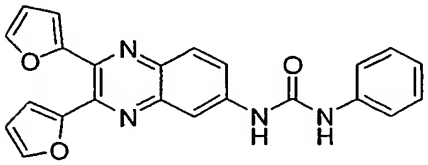
2,3-Bis-thiazol-2-yl-quinoxalin-6-ylamine. Example 12 (600 mg, 1.76 mmol) was suspended in 9 ml ethyl acetate. To this was added $SnCl_2$ (1.6 g, 7.04 mmol). The reaction mixture was heated to reflux and stirred for 2 hours. The cooled reaction solution was poured into a mixture of 100 ml saturated $NaHCO_3$ solution and ice. The resulting emulsion was filtered through celite and the organic and aqueous layers were separated. The aqueous layer was washed with 100ml ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the product (355 mg, 65%) as a brown solid which was used without further purification. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 3.3 Hz, 1H) 7.88 - 7.81 (m, 3H), 7.77 (d, J = 3.0 Hz, 1H), 7.37 (dd, J = 9.0, 2.4 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.53 (s, 2 H). ESI MS: 310 (M+1).

Example 20



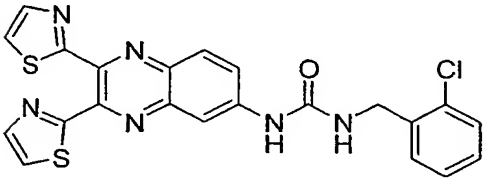
2,3-Difuran-2-yl-quinoxalin-6-ylamine. This material was prepared in a manner analogous to example 13 (7.89 g, 93%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 9.0 Hz, 1H), 7.68 (ddd, J = 6.3, 0.9, 0.9 Hz, 2H), 7.29 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 9.0, 2.4 Hz, 1H), 6.65 - 6.60 (m, 4H), 4.34 (br s, 2H). ESI MS: 278 (M+1).

Example 21: Compound 21



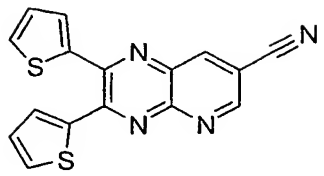
1-(2,3-Difuran-2-yl-quinoxaline-6-yl)-3-phenylurea. A suspension of phenyl isocyanate (47 mg, 0.4mmol) and the corresponding aniline starting material (100 mg, 0.36 mmol) were mixed in anhydrous toluene (4 ml) then heated to reflux and allowed to stir for 18 hours. The desired product was collected by the filtration of the cooled reaction mixture (82mg; 58%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.96 (s, 1H), 8.34 (d, J = 2.4Hz, 1H), 8.04 (d, J = 9.0Hz, 1H), 7.90 (dd, J = 6.6, 0.9Hz, 2H), 7.84 (dd, J = 9.3, 2.4Hz, 1H), 7.54 (d, J = 7.8Hz, 2H), 7.35 (dd, J = 8.4, 7.5Hz, 2H), 7.04 (dd, J = 7.2, 6.6Hz, 1H), 6.70-6.74 (m, 4H). ESI MS: 397 (M+1). The assay data yielded PI@ 25 μM = 100% and an IC_{50} = 1.35 μM.

Example 22: Compound 22



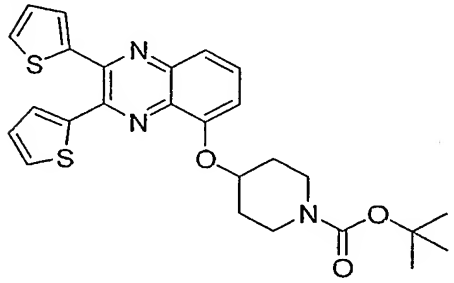
1-(2,3-Bis-thiazol-2-yl-quinoxalin-6-yl)-3-(2-chlorobenzymaticyl)-urea. This material was prepared in a similar manner to example 21 using the product from Example 19 and 2-chlorobenzymaticyl isocyanate. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.45 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 3.3 Hz, 1H), 7.99 (d, J = 3.3 Hz, 1H), 7.93 - 7.89 (m, 3H), 7.56 - 7.51 (m, 2H), 7.45 - 7.35 (m, 2H), 7.11 (t, J = 6.0 Hz, 1H), 4.51 (d, J = 6.0 Hz, 2H). ESI MS: 479 (M+1). The assay data yielded PI@ 10 μM = 65.4% and an IC_{50} = 5.80 μM.

Example 23: Compound 23



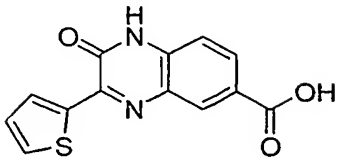
2,3-Difuran-2-yl-pyridino[2,3-*b*]pyrazine-7-carbonitrile. Example 4 (300 mg, 0.8 mmol) and Copper(I)cyanide (143 mg, 1.6 mmol) were placed in a stir bar equipped pressure tube and taken up in anhydrous DMF (5ml). The tube was sparged with argon, sealed, and heated to 130°C for 18 hours. The cooled reaction solution was partitioned between water and ethyl acetate. The combined organic layers were dried with brine, $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash column chromatography using dichloromethane as an eluant (208 mg, 41%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.57 (d, J = 2.1 Hz, 1H), 9.37 (d, J = 2.1 Hz, 1H), 8.16 – 8.11 (m, 2H), 7.65 (dd, 3.9, 0.9 Hz, 1H), 7.57 (dd, J = 3.6, 0.9 Hz, 1H), 7.37 (m, 2H). ESI MS: 321 (M+1). The assay data yielded PI@ 10 μM = 73.8% and an IC_{50} = 1.53 μM.

Example 24: Compound 24



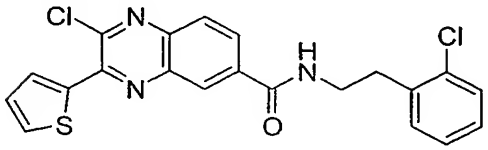
4-(2,3-dithophen-2-yl-quinoxalin-5-yloxy)-piperidine-1-carboxylic acid tert-butyl ester. Example 18 (310 mg, 1 mmol), N-BOC-4-hydroxypiperidine (201 mg, 1 mmol) and triphenylphosphine (393 mg, 1.5 mmol) were taken up in anhydrous THF and cooled to 0°C under argon. *Di-t*-butylazodicarboxylate (DBAD) (345 mg, 1.5 mmol) was added in one portion. This mixture was allowed to stir for 18 hours while coming up to room temperature. The crude reaction mixture was concentrated and applied to a flash column using 100% dichloromethane- 10% ethyl acetate in dichloromethane as the elution solvent (305 mg, 62%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 8.7, 1.2 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.45 (dd, J = 5.1, 1.2 Hz, 1H), 7.38 (dd, J = 5.1, 1.2 Hz, 1H), 7.30 (dd, J = 3.6, 1.2 Hz, 1H), 7.14 - 7.11 (m, 2H), 7.01 (dd, J = 5.1, 5.1 Hz, 1H), 6.91 (dd, J = 5.1, 4.8 Hz, 1), 4.82 (m, 1H), 3.73 (m, 2H), 3.40 (m, 2H), 1.94 (m, 4H), 1.42 (s, 9H). ESI MS: 494 (M+1). The assay data yielded PI @ 10 μM = 30.7%.

Example 25



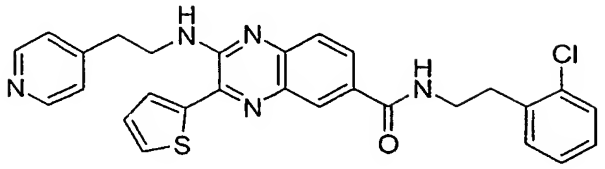
2-Oxo-3-thiophen-2-yl-1,2-dihydroquinoxaline-6-carboxylic acid. Example 17 (300 mg, 1.05 mmol) was suspended in 6 ml of methanol. Lithium hydroxide monohydrate (221 mg, 5.26 mmol) was added in one portion as a solution in 2 ml water and the resulting homogenous mixture was stirred overnight. The crude reaction mixture was concentrated and partitioned between 3N HCl and and ethyl acetate. Organic washes were dried with brine, $MgSO_4$, filtered and concentrated to a solid mixture of regioisomers (307 mg, 100%). ESI MS: 273 (M+1).

Example 26



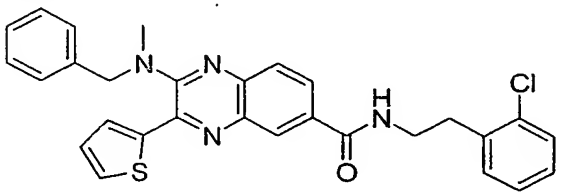
2-Chloro-3-thiophen-2-yl-6-quinoxaline carboxylic acid [2-(2-chlorophenyl)-ethyl]-amide. Example 25 (349 mg, 1.28 mmol) was taken up in 5 ml of $POCl_3$ and DMF (3 drops). After 18 hours at reflux, the crude mixture was concentrated in vacuo to a dark brown solid which was thoroughly triturated in dichloromethane. Filtration and concentration of the dichloromethane solution gave an orange solid which was taken up in fresh dichloromethane. This solution was cooled to 0°C and treated first with triethylamine (1.4 ml, 10.3 mmol) then 2-(2-chlorophenyl)-ethylamine (0.56 ml, 3.8 mmol) and then allowed to stir 1 hour. The reaction mixture was partitioned between 1N HCl and dichloromethane. The organic washes were combined and dried with brine, $MgSO_4$, filtered and concentrated. This product was isolated as an inseparable mixture of regioisomers from a flash column using 20% ethyl acetate in dichloromethane as an elution solvent (476 mg; 87%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.27 - 8.25 (m, 2H), 8.06 (dd, J = 8.7, 2.1 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.56 (dd, J = 5.1, 0.9 Hz, 1H), 7.35 - 7.32 (m, 1H), 7.22 - 7.14 (m, 4H), 3.75 (q, J = 6.9 Hz, 2H), 3.08 (t, J = 6.9 Hz, 2H). ESI MS: 477 (M+1).

Example 27: Compound 27



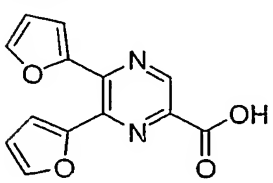
2-(2-Pyridin-4-yl-ethylamino)-3-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(2-chlorophenyl)-ethyl]-amide. A solution of Example 26 (30 mg, 0.07 mmol) and 2-pyridin-4-yl ethylamine (22 mg, 0.18 mmol) in 1 ml DMF was heated to 80°C overnight. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was treated to brine, Na_2SO_4, filtered, concentrated to a residue that was isolated as an inseparable mixture of regioisomers by preparative TLC using 10% methanol in dichloromethane as the elution solvent (18 mg; 50%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, J = 4.2, 2.1 Hz, 2H), 8.08 (d, J = 2.1 Hz, 0.5H), 7.97 (d, J = 2.1 Hz, 0.5H), 7.94 (d, J = 2.1 Hz, 0.5H), 7.85 (d, J = 8.4 Hz, 0.5H), 7.68 (dd, J = 8.4, 2.7 Hz, 1H), 7.50 - 7.42 (m, 1 H), 7.39 - 7.30 (m, 2H), 7.26 - 7.14 (m, 6H), 6.33 - 6.27 (m, 1H), 5.67 - 5.64 (m, 1H), 3.88 - 3.79 (m, 2H), 3.77 - 3.69 (m, 2H), 3.10 - 2.98 (m, 4H). ESI MS: 515 (M+1). The assay data yielded IC_{50} = 2.64 μM.

Example 28: Compound 28



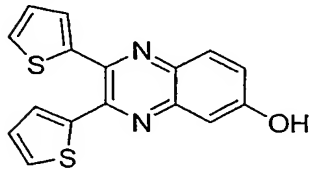
2-(Benzymaticyl-methyl-amino)-3-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(2-chlorophenyl)-ethyl]-amide. This material was prepared in manner analogous to example 27 using *N*-methylbenzymaticylamine and example 26 in the same proportions. Example 28 was isolated as an inseparable mixture of regioisomers by preparative TLC using 25% ethyl acetate in hexane as the elution solvent (27 mg; 75%): ESI MS: 513 (M+1). The assay data yielded IC_{50} = 2.32 μM.

Example 29



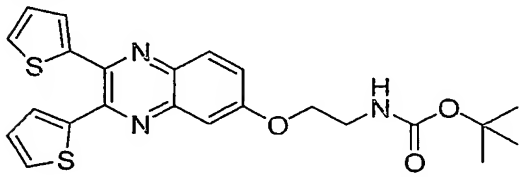
5,6-Difuran-2-yl-pyrazine-2-carboxylic acid. 2,3-diaminopropionic acid hydrochloride (466 mg, 3.3 mmol) was added in one portion to a suspension of furil (300 mg, 1.57 mmol) and crushed NaOH (377 mg, 9.42 mmol) in 26 ml of methanol. The mixture was heated to reflux for 1 hour. The cooled reaction mixture was filtered and the filtrate concentrated to an orange residue. An aqueous solution of this was taken to pH < 4 with 1N HCl and then extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated to a black glassy material which was used without further purification (342 mg; 85%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.99 (m, 2H), 6.95 (m, 2H), 6.83 (m, 2H).

Example 30



2,3-Dithiophen-2-yl-5-hydroxyquinoxaline. 2,3-Dithiophen-2-yl-5-methoxyquinoxaline (3 g, 9.3 mmol) was taken up in 20 ml 40% HBr and 20 ml glacial acetic acid, heated to 120°C and stirred for 18 hours. The cooled reaction mixture was partitioned between ice water and ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and purified with a flash column chromatography using 25% ethyl acetate in hexane as the eluant (1.92g, 67%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.92 (br s, 1H), 8.14 (d, J = 9.3 Hz, 1H), 8.03 - 7.97 (m, 2H), 7.63 (dd, J = 9.3, 2.7 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.39 - 7.32 (m, 4H). ESI MS: 311 (M+1).

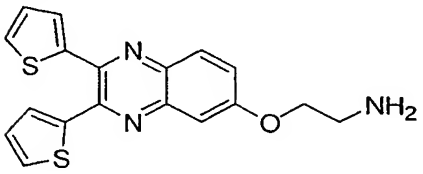
Example 31: Compound 31



[2-(2,3-Dithiophen-2-yl-quinoxalin-6-yloxy)-ethyl]-carbamic acid *tert*-butyl ester. DBAD (111 mg, 0.48 mmol) was added to a solution of Example 30 (100 mg, 0.32 mmol), N-BOC-glycinol (57 mg, 0.35 mmol) and triphenylphosphine (127 mg, 0.48 mmol) in anhydrous THF. The mixture was allowed to stir for 18 hours after which it was

concentrated in-vacuo. After purification by flash column chromatography, using 25% ethyl acetate in hexane as the eluant, a yellow oil, which crystallized upon standing, was isolated. This material was triturated with ether to isolate the final product (89 mg, 61%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 9.6 Hz, 1H), 7.29 (2dd, J = 3.3, 0.9 Hz, 2H), 7.20 - 7.17 (m, 2H), 7.03 - 7.02 (m, 2H), 6.87 - 6.83 (m, 2H), 4.83 (br m, 1H), 4.01 (t, J = 4.8 Hz, 2H), 3.45 (q, J = 4.8 Hz, 2H), 1.28 (s, 9H). ESI MS: 484 (M+MeOH). The assay data yielded PI@ 11 μM = 39.9%.

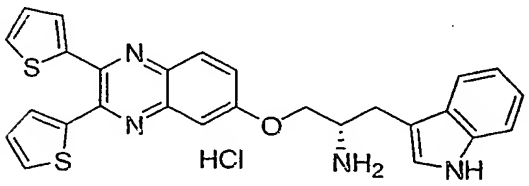
Example 32



2-(2,3-Dithiophen-2-yl-quinoxalin-6-yloxy)-ethylamine hydrochloride. Example 31 was stirred for 4 hours in 3 ml of methanol that had been saturated with hydrogen chloride. This mixture was concentrated to give the title product as the HCl salt (66 mg, 100%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.25 (br s, 2H), 8.02 (d, J = 9.3 Hz, 1H), 7.81 (2dd, J = 4.8, 0.9 Hz, 2H), 7.55 - 7.50 (m, 2H), 7.22 (2dd, J = 3.6, 1.2 Hz, 2H), 7.15 - 7.12 (m, 2H), 4.44 (t, J = 4.8 Hz, 2H), 3.34 (br m, 2H). ESI MS: 353 (M+1).

The following compounds were prepared as their HCl salts in a manner analogous to examples 30 and 31 by substituting the appropriate N-BOC protected amino alcohol for N-BOC glycinol.

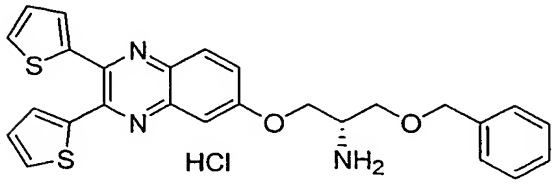
Example 33: Compound 33



(S)-2-(2,3-Dithiophen-2yl-quinoxalin-6-yloxy)-1-(1*H*-indol-3-ylmethyl)-ethylamine Hydrochloride.(119mg, 88%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.87 (d, J = 1.8 Hz, 1H), 8.26 (br s, 2H), 7.83 (d, J = 9.3 Hz, 1H), 7.61 (2dd, J = 5.1, 1.2 Hz, 2H), 7.49 (d, J = 5.8 Hz, 1H), 7.38 (dd, J = 9.3, 2.7 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.20 (d, J = 5.8 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 3.9, 1.2 Hz, 1H), 6.99 (dd, J = 3.9, 1.2

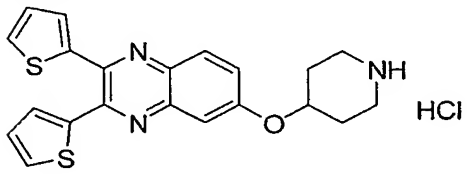
Hz, 1H), 6.95 - 6.89 (m, 3 H), 6.82 (t, J = 5.2 Hz, 1H), 4.20 (dd, J = 10.8, 3.0 Hz, 1H), 4.06 (dd, J = 10.8, 10.8, 1H), 3.68 (br m, 1H), 3.06 (m, 2H). ESI MS: 483 (M+1). The assay data yielded PI@ 11 μM = 56%.

Example 34: Compound 34



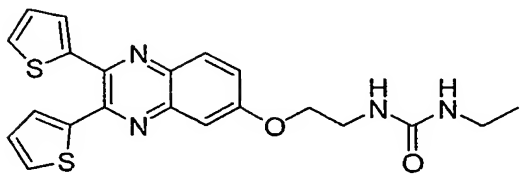
1-Benzymaticyloxymethyl-2-(2,3-dithiophen-2-yl-quinoxalin-6-yloxy)-ethylamine Hydrochloride. (17 mg, 60%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.26 (br s, 2H), 8.03 (d, J = 9.9 Hz, 1H), 7.81 (dd, J = 5.4, 0.9 Hz, 2H), 7.54 - 7.51 (m, 2H), 7.50 - 7.32 (m, 5H), 7.23 (dd, J = 3.9, 0.9 Hz, 1H), 7.20 (dd, J = 3.6, 0.9 Hz, 1H), 7.16 - 7.12 (m, 2H), 4.63 (s, 2H), 4.49 (dd, J = 10.8, 3.9 Hz, 1H), 4.40 (dd, J = 10.8, 10.8 Hz, 1H), 3.91 - 3.85 (m, 1H), 3.80 (m, 2H). ESI MS: 474 (M+1). The assay data yielded PI@11μM = 48.8%.

Example 35: Compound 35



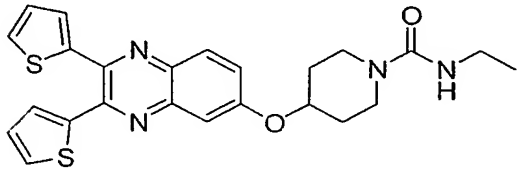
6-(Piperidin-4-yloxy)-2,3-dithiophen-2-yl-quinoxaline Hydrochloride.(132 mg, 52%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.90 (br s, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.74 (dd, J = 5.1, 0.9 Hz, 1H), 7.71 (dd, J = 5.1, 0.9 Hz, 1H), 7.52 (d, J = 2.7 Hz, 1H), 7.45 (dd, J = 9.0, 2.7 Hz, 1H), 7.15 (dd, J = 9.0, 2.7 Hz, 1H), 7.12 (dd, J = 9.0, 2.7 Hz, 1H), 7.08 - 7.05 (m, 2H), 4.94 (p, J = 3.9 Hz, 1H), 3.23 (br m, 2H), 3.11 (br m, 2H), 2.16 (br m, 2H), 1.90 (br m, 2H). ESI MS: 394 (M+1). The assay data yielded PI@ 11 μM = 45.5%.

Example 36: Compound 36



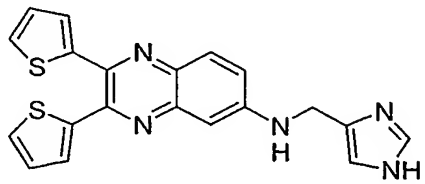
1-[2-(2,3-Dithiophen-2-yl-quinoxalin-6-yloxy)-ethyl]-3-ethyl-urea. Example 32 (30 mg, 0.08 mmol) and triethylamine (13 L, 0.09 mmol) were dissolved in dichloromethane and treated with ethyl isocyanate (7 L, 0.09 mmol). This mixture was stirred for 30 minutes after which it was poured into water and extracted with more dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by filtering through a plug of silica gel eluting with 5% methyl alcohol in dichloromethane (19 mg; 56%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 9.9 Hz, 1H), 7.41 (dd, J = 3.0, 0.9 Hz, 1H), 7.40 (dd. J = 3.0, 0.9 Hz, 1H), 7.28 - 7.25 (m, 2H), 7.13 (dd, J = 3.9, 1.2 Hz, 2H), 6.98 - 6.94 (m, 2H), 4.72 (br m, 1H), 4.32 (br m, 1H), 4.14 (t, J = 4.8 Hz, 2H), 3.64 (q, J = 5.1 Hz, 2H), 3.17 (p, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H). ESI MS: 425 (M+1). The assay data yielded PI@ 11 μM = 45.1%.

Example 37: Compound 37



4-(2,3-Dithiophen-2-yl-quinoxalin-6-yloxy)-piperidine-1-carboxylic acid ethylamide. This compound as prepared in analogous manner to Example 36 using Example 35 as the starting material (31 mg, 83%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 9.9 Hz, 1H), 7.61 (dd, J = 5.1, 0.9 Hz, 2H), 7.52 - 7.48 (m, 2H), 7.33 (td, J = 3.6, 0.9 Hz, 2H), 7.17 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 5.1 Hz, 1H), 4.85 - 4.82 (m, 1H), 4.57 (br t, 1H), 3.88 - 3.80 (m, 2H), 3.51 - 3.39 (m, 4H), 2.26 - 2.18 (m, 2H), 2.08 - 1.99 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H). ESI MS: 466 (M+1). The assay data yielded PI@ 11 μM = 33.5%.

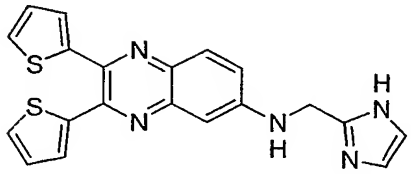
Example 38: Compound 38



2,3-Di-thiophen-6-[*N*-4(5)-methylamino-1H-imidazolyl]-2-yl-quinoxaline. In a 30 ml screw cap vial equipped with a magnetic stirrer, 6-Amino-2,3-di-thiophen-2-yl-

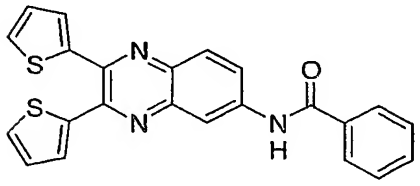
quinoxaline (100 mg, 0.323 mmol) was mixed with 4.6 ml dichloromethane followed by imidazo-4(5)-1H-carboxaldehyde (31 mg, 0.323 mmol) and glacial acetic acid (93 uL, 1.62 mmol). The reaction is stirred at r.t. for 1 h and sodium cyanoborohydride was added slowly. After stirring overnight at r.t., the reaction was added to saturated aqueous sodium bicarbonate and extracted twice with ethyl ether. Evaporation of the solvent from the combined ethereal phases affords the crude product. Purified via silica chromatography eluting with 7% methyl alcohol in dichloromethane (yield = 63%). ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.74 (d, J = 9.0 Hz, 1H), 7.7 (br s, 1H), 7.57 (dd, J = 9.0, 3.0 Hz, 1H), 7.56 (dd, J = 9.0, 3.0 Hz, 1H), 7.31 (dd, J = 9.0, 3.0 Hz, 1H), 7.09 – 7.01 (m, 5H), 6.92 (d, J = 3.0 Hz, 1H), 4.43 (br s, 2H). ESI MS: 390 (M+1).

Example 39: Compound 39



2, 3-Di-thiophen-6-[*N*-2-methylamino-1H-imidazolyl]-2-yl-quinoxaline. See the example for 2,3-Di-thiophen-6-[*N*-4(5)-methylamino-1H-imidazolyl]-2-yl-quinoxaline (example 38) for the preparation of this compound (Yield = 3%). ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.84 (d, J = 9.0 Hz, 1H), 7.45 (dd, J = 9.0, 3.0 Hz, 2H), 7.16 – 7.14 (m, 3H) 7.04 – 6.99 (m, 5H), 4.60 (br s, 2H). ESI MS: 390 (M+1).

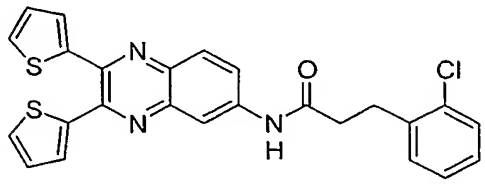
Example 40: Compound 40



N-(2,3-Di-thiophen-6-quinoxalinyl)-benzymaticamide. In a 10 ml sized vial equipped with a magnetic stirrer, the 6-Amino-2,3-di-thiophen-2-yl-quinoxaline (50 mg, 0.162 mmol), 2.3 ml of dichloromethane and triethylamine (27 μM, 0.194 mmol) were added followed by benzymaticoyl chloride (19 μM, 0.162 mmol). The reaction was stirred at r.t. overnight. Workup consisted of evaporating the solvent and purifying the mixture using normal phase chromatography eluting with 20% ethyl acetate in hexanes (yield = 52%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 3.0 Hz, 1H), 8.10 – 8.05 (m,

3H), 7.97 – 7.92 (m, 2H), 7.61 – 7.52 (m, 3H), 7.50 (dd, J = 9.0, 3.0 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.07 – 7.02 (m, 2H). ESI MS: 414 (M+1).

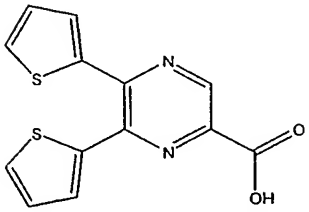
Example 41: Compound 41



2-Chloro-*N*-(2,3-di-thiophen -6-quinoxalinyl)-benzymaticenepropanamide. See example above for procedure for the preparation of this compound (Yield = 21%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.82 (dd, J = 9.0, 3.0 Hz, 1H), 7.49 (dt, J = 6.0, 2.0 Hz, 2H), 7.40 – 7.32 (m, 2H), 7.26 – 7.16 (m, 4H), 7.04 – 7.01 (m, 2H), 3.23, (t, J = 9.0 Hz, 2H), 2.79 (t, J = 9.0 Hz, 2H).

Example 42

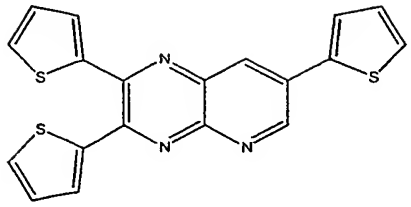
Preparation of 5,6-Di-thiophen-2-yl-pyrazin-2-carboxylic acid.



A mixture of 2,2'-Thenil (2.24 g, 10 mmol), 2,3-diaminopropionic acid (2.95 g, 21 mmol) and NaOH (2.4 g, 60 mmol) in MeOH (160 ml) was heated to reflux and stirred overnight. After cooling, the mixture was concentrated in vacuo to leave a crude residue. The residue was dissolved in H_2O (250 ml) and acidified to pH 3-4 using 1N HCl. The emerging precipitate was filtered to give an orange solid (2g). The solid was purified by column chromatography (silica gel) using EtOAc/AcOH (99:1) as an eluent and the resulting solid was triturated with EtOAc to give the title compound (1.1 g, 38%) as a solid.

Example 43: Compound 43

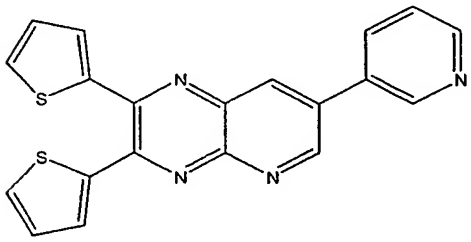
Preparation of 2,3,7-Tri-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



$PdCl_2(Ph_3P)_2$ (15 mg, 0.02 mmol) was added in one portion to a stirred solution of 7-bromo-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (124 mg, 0.34 mmol) in 1,4-dioxane (4 ml) ar rt under argon. The mixture was stirred for 5 min then 2-thiopheneboronic acid (50 mg, 0.38 mmol) was added in one portion followed by a solution of K_2CO_3 (95 mg, 0.68 mmol) in H_2O (1 ml). The mixture was heated to reflux and stirred for 90 min. After cooling, the mixture was poured into H_2O (50 ml) and EtOAc (50 ml). The aqueous and organic layers were partitioned and the aqueous layer further extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed with brine (1 x 50 ml), dried ($MgSO_4$), filtered and the mixture concentrated in vacuo to leave a crude solid. The solid was purified by column chromatography (silica gel) using hexane/EtOAc as an eluent (4:1 to 1:1) to give the title compound (90 mg, 70%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.46 (d, J = 2.4 Hz, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.03 (app. d, J = 3.6 Hz), 7.87 (app. d, J = 4.5 Hz, 2H), 7.81 (app. d, J = 5.1 Hz, 1H), 7.35 (app. d, J = 3.6 Hz, 1H), 7.27-7.31 (m, 2H), 7.13-7.18 (m, 2H). ESI MS: 378 (M +1). The assay data yielded 88% INH @ 10 μM.

Example 44: Compound 44

Preparation of 7-Pyridin-3-yl-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine

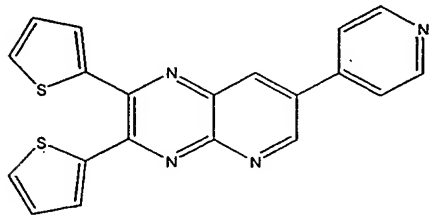


The compound was prepared using the method described for 2,3,7-tri-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using pyridyl-3-boronic acid (55 mg, 0.38 mmol) in place of 2-thiophene boronic acid. The compound was purified by column chromatography (silica gel) using hexane/EtOAc (1:1) as an eluent. The solid was then purified further using MP-TsOH (Argonaut Technologies) using the procedure below.

A cartridge containing 0.5g of MP-TsOH (Argonaut Technologies) was conditioned by washing with CH_2Cl_2 (1 x 4 ml). 7-Pyridin-3-yl-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine was loaded on to the MP-TsOH with methyl sulfoxide and the resin was washed with methyl sulfoxide (1 x 4 ml), MeOH (2 x 4 ml), THF (1 x 4 ml) and MeOH (2 x 4 ml). The compound was released from the resin by eluting with 2N NH_3 in EtOH. The solvent was concentrated in vacuo to leave the title compound (30 mg, 24%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.51 (d, J = 2.7 Hz, 1H), 9.24 (m, 1H), 8.87 (d, J = 2.7 Hz, 1H), 8.70 (dd, J = 4.8, 1.5 Hz, 1H), 8.45 (dt, J = 4.2, 0.6 Hz, 1H), 7.87-7.90 (m, 2H), 7.59-7.66 (m, 1H), 7.38-7.39 (m, 1H), 7.31-7.32 (m, 1H), 7.14-7.19 (m, 2H). ESI MS: 373 (M +1). The assay data yielded 63% @ 10 μM.

Example 45: Compound 45

Preparation of 7-Pyridin-4-yl-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine

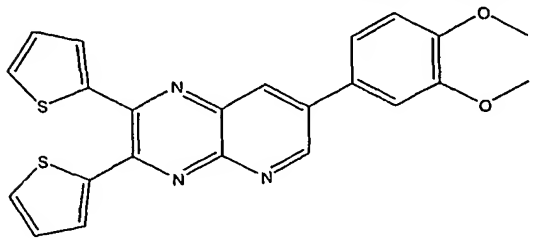


The compound was prepared using the method described for 2,3,7-tri-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using pyridyl-3-boronic acid (55 mg, 0.38 mmol) in place of 2-thiophene boronic acid. The compound was purified by column chromatography (silica gel) using hexane/EtOAc (1:1) as an eluent. The solid was then purified further using MP-TsOH (Argonaut Technologies) using the procedure below.

A cartridge containing 0.5 g of MP-TsOH (Argonaut Technologies) was conditioned by washing with CH_2Cl_2 (1 x 4 ml). 7-Pyridin-3-yl-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine was loaded on to the MP-TsOH with methyl sulfoxide and the resin was washed with methyl sulfoxide (1 x 4 ml), MeOH (2 x 4 ml), THF (1 x 4 ml) and MeOH (2 x 4 ml). The compound was released from the resin by eluting with 2N NH_3 in EtOH. The solvent was concentrated in vacuo to leave the title compound (30 mg, 24%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.58 (d, J = 2.7 Hz, 1H), 8.94 (d, J = 2.7 Hz, 1H), 8.76 (m, 2H), 8.08-8.10 (m, 2H), 7.88-7.91 (m, 2H), 7.39-7.40 (m, 1H), 7.32-7.34 (m, 1H), 7.16-7.19 (m, 2H). ESI MS: 373 (M +1). The assay data yielded 64% @ 10 μM.

Example 46: Compound 47

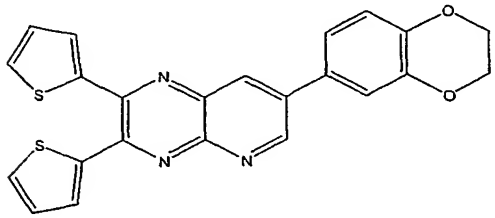
Preparation of 7-(3,4-Dimethoxy-phenyl)-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for 2,3,7-tri-thiophen-2-yl-pyrido[2,3-*b*] using 3,4-dimethoxyphenylboronic acid (72 mg, 0.38 mmol) in place of 2-thiophene boronic acid. The compound was purified by column chromatography (silica gel) using hexane/EtOAc (1:1) as an eluent to give the title compound (20 mg, 14%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.53 (d, J = 2.7 Hz, 1H), 8.74 (d, J = 2.7 Hz, 1H), 7.86-7.88 (m, 2H), 7.60-7.63 (m, 2H), 7.35-7.36 (m, 1H), 7.29-7.30 (m, 1H), 7.13-7.18 (m, 3H), 3.93 (s, 3H), 3.85 (s, 3H). ESI MS: 432 (M + 1). The assay data yielded 57% @ 10 μM.

Example 47: Compound 47

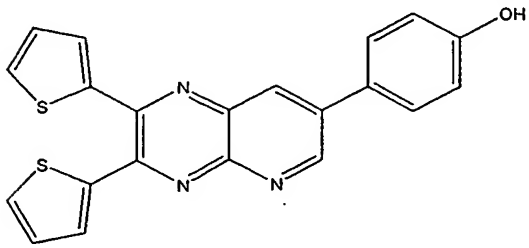
Preparation of 7-(2,3-Dihydro-benzymatico[1,4]dioxin-6-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for 2,3,7-tri-thiophen-2-yl-pyrido[2,3-*b*] using 2,3-dihydro-1,4-benzymaticodioxin-6-yl boronic acid (72 mg, 0.38 mmol) in place of 2-thiophene boronic acid. The compound was purified by column chromatography (silica gel) using hexane/EtOAc (1:1) as an eluent to give the title compound (20 mg, 14%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.45 (d, J = 2.7 Hz, 1H), 8.63 (d, J = 2.7 Hz, 1H), 7.85-7.87 (m, 1H), 7.57-7.58 (m, 1H), 7.51 (app. d, J = 2.4 Hz, 1H), 7.34-7.36 (m, 1H), 7.27-7.28 (m, 1H), 7.12-7.18 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 4.33 (s, 4H). ESI MS: 430 (M + 1). The assay data yielded 56% @ 10 μM.

Example 48: Compound 48

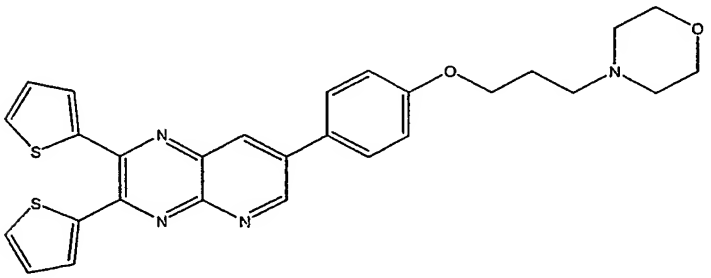
Preparation of 4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol



$PdCl_2(dppf)$ (25 mg, 0.03 mmol) was added to a stirred solution of 7-bromo-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (0.37 g, 1.0 mmol) in 1,4-dioxane (8 ml) at rt under argon. The mixture was stirred for 5 min then 4-hydroxyphenylboronic acid (0.15 g, 1.1 mmol) was added in one portion, followed by a solution of K_2CO_3 (0.28 g, 2.0 mmol) in H_2O (2 ml). The mixture was heated to reflux and stirred overnight. After allowing to cool, the mixture was poured in to H_2O (100 ml) and the emerging precipitate was filtered and washed with EtOAc to give the title compound (250 mg, 65%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.91 (br. s, 1H), 9.46 (br. s, 1H), 8.59 (br. s, 1H), 8.70-8.90 (m, 4H), 7.35 (br. s, 1H), 7.27 (br. s, 1H), 7.15 (m, 2H), 6.96-6.97 (m, 2H). ESI MS: 388 (M +1).

Example 49: Compound 49

Preparation of 7-[4-(3-Morpholin-4-yl-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



A mixture of 4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol (65 mg, 0.17 mmol), K_2CO_3 (70 mg, 0.5 mmol), 4-(3-chloro-propyl)-morpholine (50 mg, 0.34 mmol) and sodium iodide (50 mg, catalytic) in DMF (3 ml) was heated to 80 °C and stirred overnight. After cooling, the mixtured was poured in to H_2O (50 ml) and extracted with EtOAc (3 x 30 ml). The combined organic extracts were washed with brine (1 x 30 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo to leave a crude oil. The oil was dissolved in DMSO (1 ml) and loaded on to a pre-conditioned (CH_2Cl_2) MP-TsOH cartridge (0.5 g MP-TsOH; Argonaut Technologies). The MP-TsOH was washed

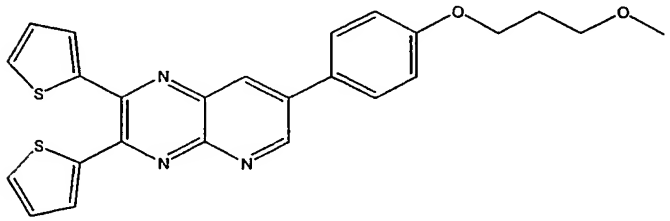
with MeOH (2 x 6 ml) and the compound released from the resin using 2N NH_3/EtOH as an eluent. Removal of the solvent in vacuo gave the title compound (70 mg, 81%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.48 (d, J = 2.7 Hz, 1H), 8.65 (d, J = 2.7 Hz, 1H), 7.97-8.06 (m, 2H), 7.86-7.88 (m, 2H), 7.35-7.36 (m, 1H), 7.28-7.29 (m, 1H), 7.14-7.18 (m, 4H), 4.07 (t, J = 7.2 Hz, 2H), 3.57 (m, 4H), 2.37-2.49 (m, 6H), 1.89-1.96 (m, 2H). ESI MS: 515 (M + 1). The assay data yielded 82% @ 10 μM.

Preparation of hydrochloride salt

HCl in 1,4-dioxane (0.5 M; 0.25 mmol, 0.13 mmol [0.5 M HCl in 1,4-dioxane prepared by addition of 1 ml 4M HCl in 1,4-dioxane to 7 ml of 1,4-dioxane]) was added to a hot solution of 7-[4-(3-morpholin-4-yl-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (65 mg, 0.13 mmol) in MeOH (15 ml). After cooling, the mixture was concentrated in vacuo to leave a solid. The solid was triturated with Et_2O then the mixture concentrated in vacuo to leave the title compound as a solid. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.52-9.53 (m, 1H), 9.13-9.14 (m, 1H), 7.95-7.97 (m, 2H), 7.84-7.85 (m, 1H), 7.83 (m, 1H), 7.56-7.59 (m, 2H), 7.13-7.24 (m, 4H), 4.24 (t, 2H), 4.09-4.14 (m, 2H), 3.82-3.90 (m, 2H), 3.60-3.64 (m, 2H), 3.43-3.49 (m, 2H), 3.20-3.31 (m, 2H), 2.33-2.41 (m, 2H). ESI MS: 515 (M + 1). The assay data yielded 83% @ 10 μM.

Example 50: Compound 50

Preparation of 7-[4-(3-methoxy-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine

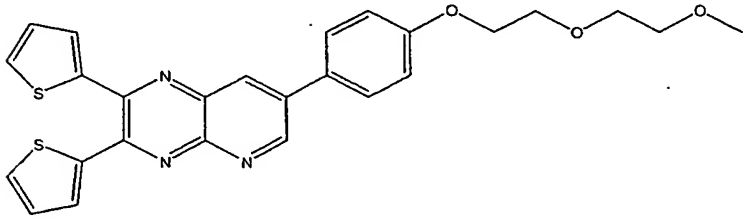


A mixture of 4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol (65 mg, 0.17 mmol), K_2CO_3 (70 mg, 0.5 mmol) and 1-bromo-3-methoxy-propane (52 mg, 0.34 mmol) in DMF (3 ml) was heated to 105 °C and stirred overnight. After cooling, the mixture was poured in to H_2O (50 ml) and extracted with EtOAc (3 x 30 ml). The combined organic extracts were washed with brine (1 x 30 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo to leave a crude oil. The oil was purified by column chromatography (silica gel) using hexane/EtOAc (9:1 to 7:3) as an eluent to give the title

compound (50 mg, 65%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.66 (d, J = 2.7 Hz, 1H), 8.32 (d, J = 2.7 Hz, 1H), 8.16-8.19 (m, 2H), 8.03-8.05 (m, 2H), 7.52-7.54 (m, 1H), 7.45-7.46 (m, 1H), 7.29-7.36 (m, 4H), 4.28 (t, J = 6.3 Hz, 2H), 3.66 (t, J = 6.3 Hz, 2H), 3.45 (s, 3H), 2.13-2.17 (m, 2H). ESI MS: 460 (M + 1). The assay data yielded 93% @ 10 μM.

Example 51: Compound 51

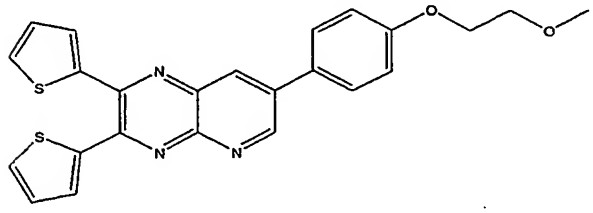
Preparation of 7-{4-[2-(2-Methoxy-ethoxy)-ethoxy]-phenyl}-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



A mixture of 4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol (97 mg, 0.25 mmol), K_2CO_3 (105 mg, 0.75 mmol) and 1-bromo-2-(methoxy-ethoxy)-ethane (92 mg, 0.5 mmol) in DMF (4 ml) was heated to 90°C and stirred overnight. After cooling, the mixture was poured in to H_2O (75 ml) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with brine (1 x 50 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo to leave a crude oil. The oil was purified by column chromatography (silica gel) using hexane/EtOAc (4:1 to 1:1) as an eluent to give the title compound (70 mg, 60%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.43 (d, J = 2.7 Hz, 1H), 8.60 (d, J = 2.7 Hz, 1H), 7.93 (m, 2H), 7.79-7.81 (m, 2H), 7.28-7.30 (m, 1H), 7.21-7.23 (m, 1H), 7.06-7.11 (m, 4H), 4.12-4.15 (m, 2H), 3.71-3.74 (m, 2H), 3.54-3.57 (m, 2H), 3.40-3.43 (m, 2H), 3.20 (s, 3H). ESI MS: 490 (M + 1). The assay data yielded 30% @ 10 μM.

Example 52: Compound 52

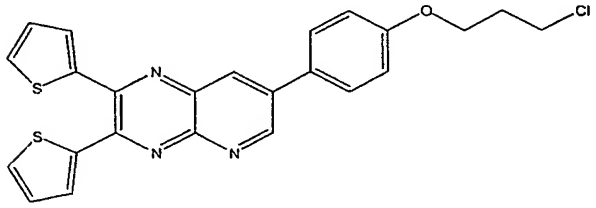
Preparation of 7-[4-(2-Methoxy-ethoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for 7-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using 1-bromo-2-methoxy-ethane (70 mg, 0.5 mmol) in place of 1-bromo-2-(methoxy-ethoxy)-ethane. The compound was purified by column chromatography (silica gel) using hexane/EtOAc (4:1 to 3:2) as an eluent to give the title compound (60 mg, 54%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.39 (d, J = 2.7 Hz, 1H), 8.56 (d, J = 2.7 Hz, 1H), 7.86-7.91 (m, 2H), 7.75-7.77 (m, 2H), 7.25-7.26 (m, 1H), 7.17-7.19 (m, 1H), 7.03-7.08 (m, 4H), 4.09-4.12 (m, 2H), 3.59-3.62 (m, 2H), 3.27 (s, 3H). ESI MS: 446 (M +1). The assay data yielded 76% @ 10 μM.

Example 53

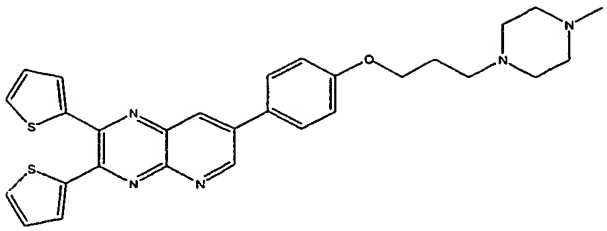
Preparation of 7-[4-(3-Chloro-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



A mixture of 4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol (0.39 g, 1.0 mmol), K_2CO_3 (0.42 g, 3.0 mmol) and toluene-4-sulfonic acid 3-chloro-propyl ester in DMF (10 ml) under argon was heated to 100 °C and stirred for 60 min. After cooling, the mixture was poured in to H_2O (150 ml) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with brine (1 x 50 ml), dried ($MgSO_4$), filtered and the mixture concentrated in vacuo to leave a crude oil. The oil was purified by column chromatography (silica gel) using hexane/EtOAc (9:1 to 7:3) then EtOAc as an eluent to give the title compound (0.4 g, 86%) as an oil. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.50 (d, J = 2.7 Hz, 1H), 8.58 (d, J = 2.7 Hz, 1H), 8.00-8.03 (m, 2H), 7.87-7.89 (m, 2H), 7.36-7.37 (m, 1H), 7.29-7.30 (m, 1H), 7.14-7.19 (m, 4H), 4.20 (t, J = 6.0 Hz, 2H), 3.80 (t, J = 6.0 Hz, 2H), 2.19-2.29 (m, 2H). ESI MS: 464 (M+1).

Example 54: Compound 54

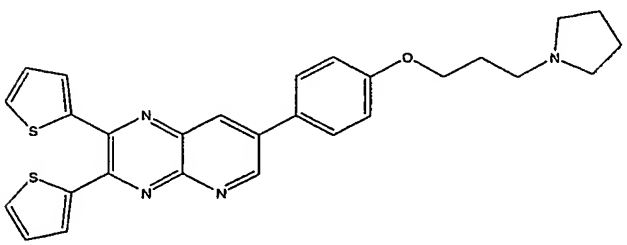
Preparation of 7-{4-[3-(4-Methyl-piperazin-1-yl)-propoxy]-phenyl}-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



A mixture of 7-[4-(3-chloro-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (47 mg, 0.1 mmol), $^{i}Pr_2NEt$ (35 L, 0.2 mmol) and *N*-methylpiperazine (25 L, 0.2 mmol) in DMSO (2 ml) was heated to 90 °C and stirred overnight. Further N-methylpiperazine (25 L, 0.2 mmol) followed by a catalytic amount of NaI was added and the mixture was heated to 105 °C and stirred for 3 hr. After cooling, the mixture (incomplete product formation by thin-layer chromatography) was poured in to H_2O (50 ml) and extracted with EtOAc (3 x 25 ml). The combined organic extracts were washed with brine (1 x 25 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude oil. The oil was purified by preparative thin-layer chromatography using EtOAc/MeOH/NH_4OH (90:9:1) as an eluent to give an impure solid. The solid was dissolved in DMSO and purified by MP-TsOH (0.5 g TsOH; Argonaut Technologies) ion exchange chromatography washing the MP-TsOH with MeOH (2 x 4 ml) and eluting with 2M NH_3/EtOH. Final purification by preparative thin-layer chromatography using EtOAc/MeOH/NH_4OH (180:19:1) as an eluent gave the title compound (20 mg, 38%) as a solid. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.21 (d, J = 2.4 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H), 7.69-7.22 (m, 2H), 7.60-7.61 (m, 2H), 7.24-7.27 (m, 2H), 6.97-7.02 (m, 4H), 4.00 (t, 2H), 2.54-2.6 (m, 10H), 2.34 (s, 3H), 1.87-1.97 (m, 2H). ESI MS: 528 (M + 1). The assay data yielded 38% @ 10 μM.

Example 55: Compound 55

Preparation of 7-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine

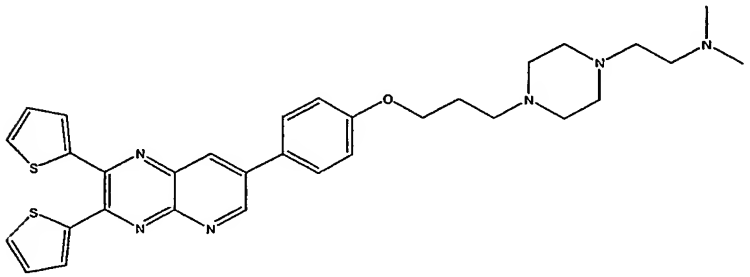


A mixture of 7-[4-(3-chloro-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (70 mg, 0.15 mmol), K_2CO_3 (62 mg, 0.45 mmol) and pyrrolidine (15 L, 0.18

mmol) in DMF (3 ml) was heated to 90 °C and stirred overnight. After cooling, the mixture was purified by MP-TsOH ion exchange chromatography (0.5 g MP-TsOH; Argonaut Technologies) washing the MP-TsOH with MeOH (3 x 4 ml) and eluting with 2M NH_3/EtOH to give the title compound (20 mg, 27%) as a solid. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.22 (d, J = 2.4 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 7.70-7.32 (m, 2H), 7.60-7.61 (m, 2H), 7.25-7.27 (m, 2H), 6.97-7.02 (m, 4H), 4.00 (t, J = 6.2 Hz, 2H), 2.59 (m, 2H), 2.50-2.52 (m, 4H), 1.91-2.00 (m, 2H), 1.73-1.77 (m, 4H). The assay data yielded 70% @ 10 μM.

Example 56: Compound 56

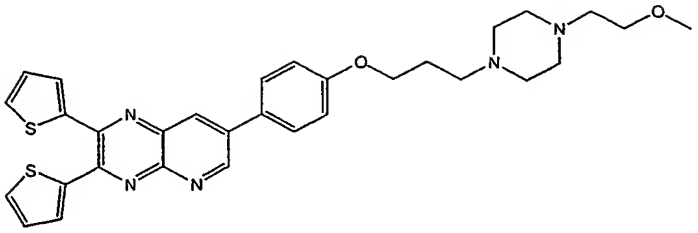
Preparation of [2-(4-{3-[4-(2,3-Di-thiophen-2-yl-pyrido[2,3-*b*]pyrazin-7-yl)-phenoxy]-propyl}-piperazin-1-yl)-ethyl]-dimethyl-amine



The compound was prepared using the method described for 7-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using dimethyl-(2-piperazin-1-yl-ethyl)-amine (30 mg, 0.18 mmol) in place of pyrrolidine. After purification by MP-TsOH the compound was further purified by preparative thin-layer chromatography using EtOAc/MeOH/NH_4OH (90:9:1) as an eluent to give the title compound (20 mg, 23%) as a solid. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.23 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 2.4 Hz, 1H), 7.72-7.75 (m, 2H), 7.59-7.61 (m, 2H), 7.24-7.26 (m, 2H), 6.96-7.03 (m, 4H), 4.00 (t, J = 6.2 Hz, 2H), 2.73 (t, J = 5.0 Hz, 2H), 2.34-2.52 (m, 12 H), 2.18 (s, 3H), 2.17 (s, 3H), 1.92-1.97 (m, 2H). The assay data yielded 37% @ 10 μM.

Example 57: Compound 57

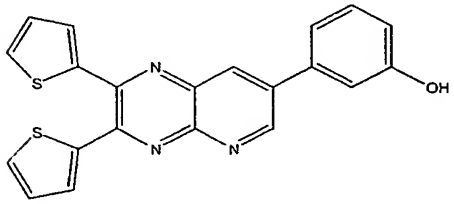
Preparation of 7-(4-{3-[4-(2-Methoxy-ethyl)-piperazin-1-yl]-propoxy}-phenyl)-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for 7-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using 1-(2-methoxy-ethyl)-piperazine (30 mg, 0.18 mmol) in place of pyrrolidine. After purification by MP-TsOH the compound was further purified by preparative thin-layer chromatography using EtOAc/MeOH/NH_4OH (90:9:1) as an eluent to give the title compound (20 mg, 23%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.48 (d, J = 2.7 Hz, 1H), 8.65 (d, J = 2.7 Hz, 1H), 7.97-8.00 (m, 2H), 7.86-7.87 (m, 2H), 7.34-7.36 (m, 1H), 7.27-7.29 (m, 1H), 7.13-7.18 (m, 4H), 4.07 (t, J = 6.0 Hz, 2H), 3.39 (t, J = 6.0 Hz, 2H), 3.22 (s, 3H), 2.40-2.49 (m, 12H), 1.85-1.94 (m, 2H). The assay data yielded 49% @ 10 μM.

Example 58

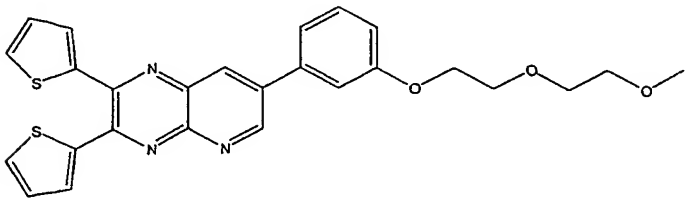
Preparation of 3-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol



$PdCl_2$(dppf) (82 mg, 0.1 mmol) was added to a mixture of 7-bromo-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (1.5 g, 4.0 mmol) in 1,4-dioxane (32 ml) at room temperature under argon. The mixture was stirred for 5 min then 3-hydroxyphenyl boronic acid (0.6 g, 4.4 mmol) was added in one portion followed by a solution of K_2CO_3 (1.1 g, 8.0 mmol) in H_2O (8 ml). The mixture was heated to reflux and stirred overnight. After cooling, the mixture was poured in to H_2O (300 ml) and extracted with EtOAc (3 x 200 ml). The combined organic extracts were washed with brine (1 x 150 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to leave the title compound (1.2 g, 77%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 9.41 (d, J = 2.4 Hz, 1H), 8.61 (d, J = 2.4 Hz, 1H), 7.87 (d, J = 4.5 Hz, 2H), 7.28-7.34 (m, 5H), 7.13-7.19 (m, 2H), 6.91-6.94 (m, 1H). ESI MS: 388 (M+1).

Example 59: Compound 59

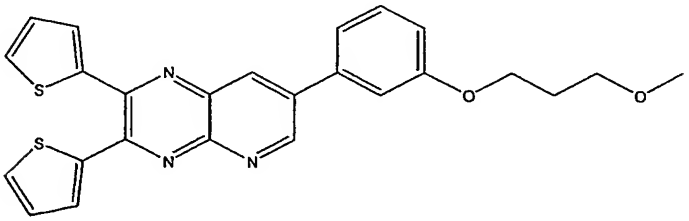
Preparation of 7-{3-[2-(2-Methoxy-ethoxy)-ethoxy]-phenyl}-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for 7-{4-[2-(2-Methoxy-ethoxy)-ethoxy]-phenyl}-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using 3-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol in place of 4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol. The compound was purified by column chromatography (silica gel) using hexane/EtOAc (4:1 to 1:1) as an eluent to give the title compound (60 mg, 49%) as a solid. ^{1}H-NMR (300 MHz, Acetone-d_6) δ 9.35 (br s, 1H), 8.47 (d, J = 2.4 Hz, 1H), 7.71-7.73 (m, 2H), 7.35-7.46 (m, 5H), 7.00-7.10 (m, 3H), 4.25-4.27 (m, 2H), 3.83-3.87 (m, 2H), 3.66-3.69 (m, 2H), 3.50-3.54 (m, 2H), 3.30 (s, 3H). ESI MS: 490 (M+1). The assay data yielded 34% @ 10 μM.

Example 60: Compound 60

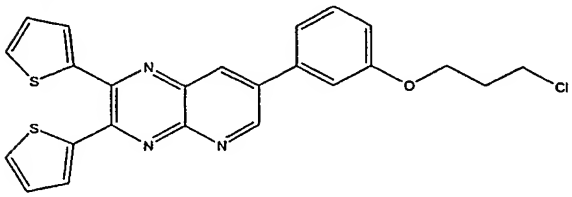
Preparation of 7-[3-(2-Methoxy-ethoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine .



The compound was prepared using the method described for 7-{4-[2-(2-Methoxy-ethoxy)-ethoxy]-phenyl}-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using 3-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol (97 mg, 0.25 mmol), K_2C0_3(105 mg, 0.75 mmol) and 1-bromo-3-methoxy-propane (50 L, 0.5 mmol) in DMF (4 ml). The compound was purified by column chromatography (silica gel) using hexane/EtOAc (4:1) as an eluent to give the title compound (70 mg, 61%) as a solid. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.09 (d, J = 2.4 Hz, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.55-7.58 (m, 2H), 7.18-7.31 (m, 5H), 6.81-6.87 (m, 3H), 3.99 (t, J = 6.3 Hz, 2H), 3.47 (t, J = 6.3 Hz, 2H), 1.89-1.99 (m, 2H). ESI MS: 460 (M + 1). The assay data yielded 37% @ 10 μM.

Example 61

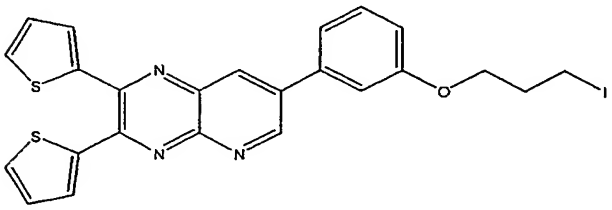
Preparation of 7-[3-(3-Chloro-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for 7-[4-(3-chloro-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using 3-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenol (0.75 g, 2.0 mmol), K_2CO_3 (0.84 g, 6.0 mmol) and toluene-4-sulfonic acid 3-chloro-propyl ester (0.75 g, 3.0 mmol) in DMF (20 ml). The compound was purified by column chromatography (silica gel) using hexane/EtOAc (4:1 to 1:1) as an eluent to give the title compound (0.85 g, 93%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.55 (d, J = 2.4 Hz, 1H), 8.81 (d, J = 2.4 Hz, 1H), 7.91-7.93 (m, 2H), 7.64-7.65 (m, 2H), 7.51 (t, J = 6.3 Hz, 1H), 7.41-7.42 (m, 1H), 7.34-7.36 (m, 1H), 7.13-7.23 (m, 3H), 4.29 (t, J = 6.0 Hz, 2H), 3.87 (t, J = 6.0 Hz, 2H), 2.23-2.31 (m, 2H). ESI MS: 464 (M + 1).

Example 62

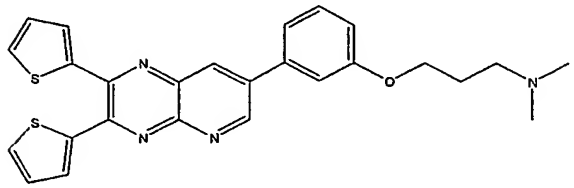
Preparation of 7-[3-(3-Iodo-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



A mixture of NaI (0.55 g, 3.7 mmol) and 7-[3-(3-chloro-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (0.85 g, 1.8 mmol) in 2-butanone (20 ml) was heated to reflux and stirred overnight (a dark reaction mixture develops). After cooling, the mixture was poured in to H_2O (75 ml) and extracted with EtOAc (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to leave the title compound (0.4 g, 40%) as an oil. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.49 (d, J = 2.4 Hz, 1H), 8.75 (d, J = 2.4 Hz, 1H), 7.86-7.87 (m, 2H), 7.58-7.65 (m, 2H), 7.48 (m, 1H), 7.35 (m, 1H), 7.28-7.30 (m, 1H), 7.06-7.18 (m, 3H), 4.15 (t, J = 6.7 Hz, 2H), 3.41 (t, J = 6.7 Hz, 2H), 2.21-2.29 (m, 2H).

Example 63: Compound 63

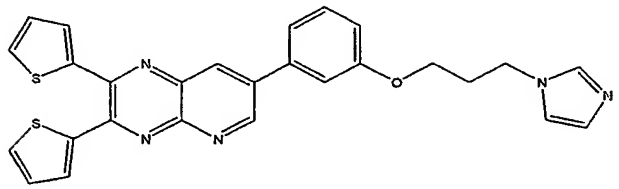
Preparation of {3-[3-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-phenoxy]-propyl}-dimethyl-amine



A solution of dimethylamine in THF (2.0 M; 1 ml, 2.0 mmol) was added to a mixture of 7-[3-(3-iodo-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (100 mg, 0.18 mmol) and Et_3N (70 L, 0.5 mmol) in DMSO (2 Ml) then heated to 90 °C for 4 hr. After cooling, the mixture was poured in to H_20 (100 ml) and extracted with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (1 x 50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude oil. The oil was purified by column chromatography (silica gel) using EtOAc/2M NH_3 in EtOH (19:1) as an eluent to give the title compound (50 mg, 59%) as a solid. ^{1}H-NMR (300 MHz, CD_3CN) δ 9.22 (d, J = 2.4 Hz, 1H), 8.39 (d, J = 2.4 Hz, 1H), 7.57-7.58 (m, 2H), 7.19-7.38 (m, 5H), 6.90-7.02 (m, 3H), 4.01 (t, J = 5.7 Hz, 2H), 2.43 (s, 6H), 2.31 (t, J = 7.1 Hz, 2H), 1.79-1.91 (m, 2H). ESI MS: 473 (M + 1). The assay data yielded 59% @ 3.7 μM and 82% @ 33 μM.

Example 64: Compound 64

Preparation of 7-[3-(3-Imidazol-1-yl-propoxy)-phenyl]2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine

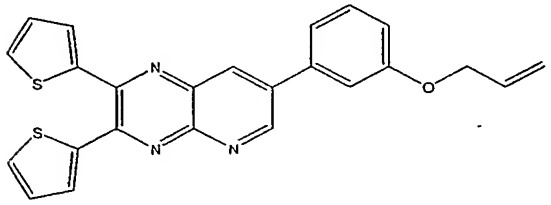


Imidazole (61 mg, 0.9 mmol) was added in one portion to a mixture of NaH (60% in mineral oil; 40 mg, 1.0 mmol) in DMF (5 ml) at room temperature under argon. The mixture was stirred for 45 min then 7-[3-(3-iodo-propoxy)-phenyl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (100 mg, 0.18 mmol) in DMSO (1 ml) was added and the mixture heated to 80 °C for 4 hr. After cooling, the mixture was poured in to H_20 (100 ml) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with brine (1 x 50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude oil.

The oil was purified by column chromatography (silica gel) using EtOAc/2M NH_3 in EtOH (19:1) as an eluent to give a solid. The solid was further purified by MP-TsOH ion exchange chromatography (0.5 g TsOH; Argonaut Technologies) washing with MeOH (2 x 4 ml) and eluting with 2M NH_3/EtOH. Finally, the compound was purified by preparative thin-layer chromatography using EtOAc/MeOH (19:1) as an eluent to give the title compound (10 mg, 11%) as a solid. ^{1}H-NMR (300 MHz, CD_3CN) δ 9.28 (d, J = 2.7 Hz, 1H), 8.50 (d, J = 2.7 Hz, 1H), 7.58-7.60 (m, 2H), 7.21-7.42 (m, 6H), 6.93-7.04 (m, 4H), 6.85 (s, 1H), 4.10 (t, J = 6.0 Hz, 2H), 3.94 (t, J = 6.0 Hz, 2H), 1.85-1.89 (m, 2H). ESI MS: 496 (M + 1). The assay data yielded 54% @ 11 μM.

Example 65: Compound 65

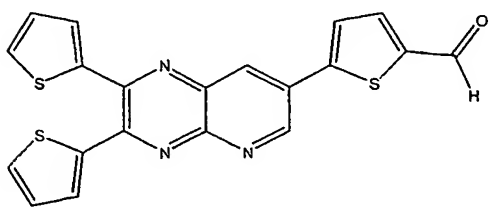
Preparation of 7-(3-Allyloxy-phenyl)-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for 7-[3-(3-imidazol-1-yl-propoxy)-phenyl]2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine using 2-(2-methoxy-ethoxy)-ethanol (70 ml, 0.9 mmol) in place of imidazole. The compound was purified by column chromatography (silica gel) using hexane/EtOAc (4:1) as an eluent to give the title compound (30 mg, 39%) a solid. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.15 (d, J = 2.4 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.58-7.61 (m, 2H), 7.24-7.38 (m, 5H), 6.92-7.01 (m, 3H), 5.95-6.07 (m, 1H), 5.32 (dq, J = 18.0, 1.6 Hz, 1H), 5.17 (dq, J = 10.8, 1.5 Hz, 1H), 4.54 (dt, J = 5.4, 1.1 Hz, 2H). ESI MS: 428 (M + 1). The assay data yielded 22% @ 10 μM.

Example 66

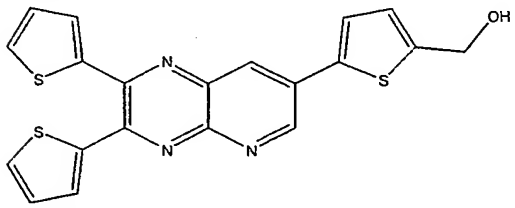
Preparation of 5-(2,3-Di-thiophen-2-yl-pyrido[2,3-*b*]pyrazin-7-yl)-thiophene-2-carbaldehyde



$PdCl_2(Ph_3P)_2$ (0.7 g, 1.0 mmol) was added in one portion to a mixture of 7-bromo-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (3.7 g, 10 mmol) in 1,4-dioxane (80 ml) at room temperature under argon. After 5 min 5-formyl-2-thiophene boronic acid (1.7 g, 11 mmol) was added in one portion followed by a solution of K_2CO_3 (2.8 g, 20 mmol) in H_2O (20 ml) then the mixture was heated to reflux overnight. After cooling, the mixture was poured in to H_2O (400 ml) and EtOAc (250 ml) then filtered. The filtrate was partitioned and the aqueous layer was extracted with EtOAc (2 x 250 ml) and the combined organic extracts washed with brine (1 x 150 ml), dried ($MdSO_4$), filtered and concentrated in vacuo to leave the title compound (3.1 g, 76%) as a crude solid that was used without further purification. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.99 (s, 1H), 9.54 (d, J = 2.4 Hz, 1H), 8.80 (d, J = 2.4 Hz, 1H), 8.19 (d, J = 3.9 Hz, 1H) 8.15 (d, J = 3.9 Hz, 1H), 7.89-7.10 (m, 2H), 7.38-7.40 (m, 2H), 7.12-7.20 (m, 2H). ESI MS: 406 (M + 1).

Example 67

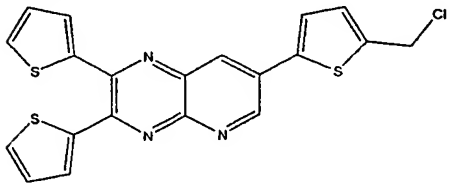
Preparation of [5-(2,3-Di-thiophen-2-yl-pyrido[2,3-*b*]pyrazin-7-yl)-thiophen-2-yl]-methanol



$NaBH_4$ (1.8 g, 47 mmol) was added in one portion to a mixture of 5-(2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazin-7-yl)-thiophene-2-carbaldehyde (1.9 g, 4.7 mmol) in EtOH (60 ml) at room temperature. The mixture was stirred overnight then poured in to 0.5 N HCl (250 ml) and extracted with EtOAc (3 x 150 ml). The combined organic extracts were washed with brine (1 x 100 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude solid. The solid was purified by column chromatography (silica gel) using hexane/EtOAc (7:3 to 1:1) as an eluent to give the title compound (0.7 g, 37%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.47 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 7.86-7.88 (m, 3H), 7.35-7.36 (m, 1H), 7.27-7.29 (m, 1H), 7.10-7.18 (m, 3H), 5.67 (t, J = 5.7 Hz, 1H), 4.71 (d, J = 5.7 Hz, 2H).

Example 68

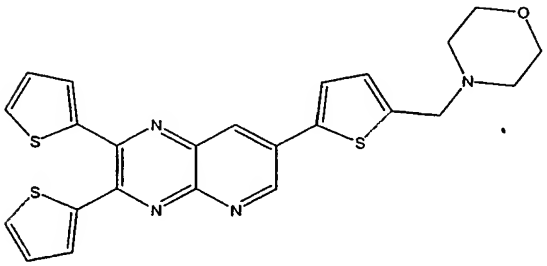
Preparation of 7-(5-Chloromethyl-thiophen-2-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



Concentrated HCl (5 ml) was added to [5-(2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazin-7-yl)-thiophen-2-yl]-methanol (500 mg, 1.25 mmol) in CH_2Cl_2 (40 ml) at room temperature and the mixture stirred overnight. CH2Cl2 (50 ml) and H_2O (50 ml) was added and the mixture partitioned. The aqueous layer was extracted with CH_2Cl_2 (1 x 50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude solid. The solid was purified by column chromatography (silica gel) using hexane/EtOAc (19:1 to 1:1) as an eluent to give the title compound (150 mg, 29%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.63 (d, J = 2.7 Hz, 1H), 8.79 (d, J = 2.7 Hz, 1H), 8.03-8.08 (m, 3H), 7.51-7.54 (m, 2H), 7.46-7.47 (m, 1H), 7.26-7.35 (m, 2H), 5.30 (s, 2H).

Example 69: Compound 69

Preparation of 7-(5-Morpholi-4-ylmethyl-thiophen-2-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine

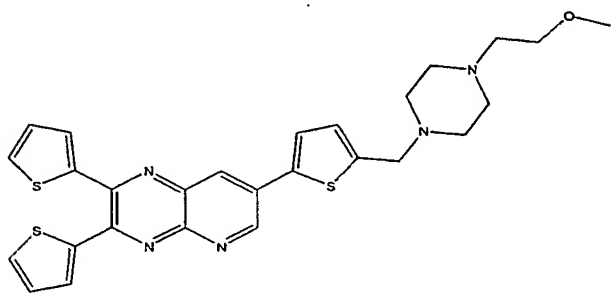


A mixture of 7-(5-chloromethyl-thiophen-2-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine (70 mg, 0.16 mmol), morpholine (30 L, 0.32 mmol) and Et_3N (70 L, 0.5 mmol) in DMSO (2 ml) was heated to 100 °C and stirred for 4 hr. After cooling, the mixture was poured in to H_2O (75 ml) and extracted with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (1 x 30 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude solid. The solid was purified by column chromatography (silica gel) using hexane/EtOAc (7:3 to 2:3) as an eluent to give the title compound (55 mg, 71%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.52 (d, J = 2.7

Hz, 1H), 8.62 (d, J = 2.7 Hz, 1H), 7.93-7.95 (m, 3H), 7.41-7.43 (m, 1H), 7.35-7.36 (m, 1H), 7.19-7.24 (m, 3H), 3.82 (s, 2H), 3.66-3.69 (m, 4H), 2.54-2.55 (m, 4H). ESI MS: 477 (M + 1). The assay data yielded 25% @ 11 μM.

Example 70: Compound 70

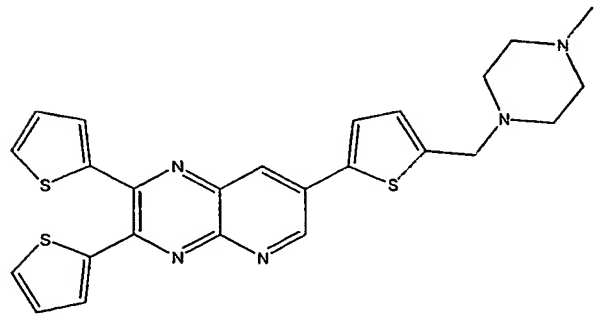
Preparation of 7-{5-[4-(2-Methoxy-ethyl)-piperazin-1-ylmethyl]-thiophen-2-yl}-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



The compound was prepared using the method described for using 1-(2-methoxy-ethyl)-piperazine (46 mg, 0.32 mmol) in place of morpholine. The compound was purified by column chromatography (silica gel) using EtOAc/2M NH_3 in EtOH (49:1 to 47:3) as an eluent to give the title compound (50 mg, 57%) as a solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.40 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 2.4 Hz, 1H), 7.82-7.83 (m, 3H), 7.30-7.32 (m, 1H), 7.23-7.25 (m, 1H), 7.06-7.13 (m, 3H), 3.70 (s, 2H), 3.51 (t, J = 5.8 Hz, 2H), 3.18 (s, 3H), 2.40-2.46 (m, 10H). ESI MS: 534 (M + 1). The assay data yielded 38% @ 11 μM.

Example 71: Compound 71

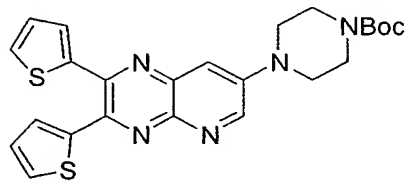
Preparation of 7-[5-(4-Methyl-piperazin-1-ylmethyl)-thiophen-2-yl]-2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazine



A mixture of $NaBH(OAc)_3$ (85 mg, 0.4 mmol), 5-(2,3-di-thiophen-2-yl-pyrido[2,3-*b*]pyrazin-7-yl)-thiophene-2-carbaldehyde (100 mg, 0.25 mmol) and *N*-methylpiperazine (30 μL, 0.25 mmol) in 1,2-dichloroethane (5 ml) was stirred at room temperature

overnight. 1N NaOH (10 ml) was added and the mixture was stirred vigerously for 60 min. CH_2Cl_2 (25 ml) and H_2O (25 ml) was added, the mixture partitioned and the aqueous layer extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to leave a crude oil. The oil was purified by preparative thin-layer chromatography using EtOAc/MeOH/NH_4OH (90:9:1) as an eluent to give a solid. The compound was purified further by MP-TsOH ion exchange chromatography (0.5 g MP-TsOH; Argonaut Technologies) washing with MeOH (2 x 4 ml) then eluting with 2M NH3/EtOH. Finally, the compound was purified by preparative thin-layer chromatography EtOAc/MeOH/NH_4OH (90:9:1) as an eluent to give the title compound (25 mg, 21%) as a solid. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 8.97 (m, 1H), 8.10 (m, 1H), 7.54-7.56 (m, 2H), 7.30-7.32 (m, 1H), 7.18-7.20 (m, 2H), 7.85-7.92 (m, 2H), 7.78-7.80 (m, 1H), 3.60 (s, 2H), 2.23-2.52 (m, 8H), 2.20 (s, 3H). ESI MS: 490 (M + 1). The assay data yielded 84% @ 10 μM.

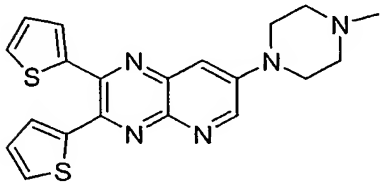
Example 72



7-Bromo-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine (4.17 mmol, 1.56g), piperazine-1-carboxylic acid tert-butyl ester (6.2 mmol, 1.16 g), tetrakis(triphenylphosphine)palladium (0.04 mmol, 48mg), and cesium carbonate (5.8 mmol, 1.9 g) were dissolved in anhydrous *N,N*-dimethyl-formamide (41 ml) and left to stir in an $Ar_{(g)}$ purged flask at 65^{0}C overnight. *N,N*-dimethyl-formamide was then removed in vacuo. The residue was dissolved in CH_2Cl_2 (20 ml), washed with water, dried with Na_2SO_4, filtered and concentrated.

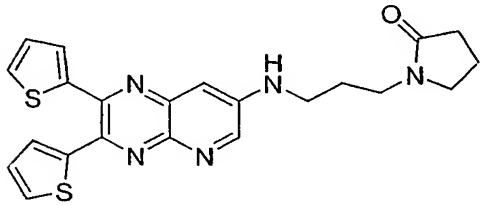
4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazine-1-carboxylic acid tert-butyl ester: Purified by flash chromatography (7:3 Hexanes/EtOAc) yielding (45% Yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.90 (d, J= 2.4 Hz, 1H), 7.45-7.43 (m, 2H), 7.41 (dd, J= 6, 3 Hz, 1H), 7.27 (dd, J= 2.4, 1.2 Hz, 1H), 7.21 (dd, J= 2.7, 0.9 Hz, 1H), 7.09 (dd, J= 3, 1.5 Hz, 1H), 6.94 (dd, J= 2.1, 1.2 Hz, 1H), 3.62 (t, J= 5.1 Hz, 4H), 3.35 (t, J= 3 Hz, 4H), 1.43 (s, 9H). ESI MS: 480 (M+1).

Example 73: Compound 73



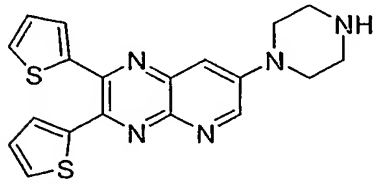
7-(4-Methyl-piperazin-1-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine: Purified by preparatory TLC (9:11) Hexane/EtOAc). 19% Yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.90 (d, J= 3.0 Hz 1H), 7.45-7.43 (m, 2H), 7.41 (dd, J= 3.9, 1.2 Hz, 1H), 7.25 (dd, J= 2.4, 1.2 Hz, 1H), 7.21 (dd, J= 2.7, 0.9 Hz, 1H), 7.00 (dd, J= 3, 1.5 Hz, 1H), 6.94 (dd, J= 2.1, 1.8 Hz, 1H), 3.44 (t, J= 6.3 Hz, 4H), 2.61 (br s, 4H), 2.34 (s, 3H). ESI MS: 394 (M+1). The assay data yielded PI @ 10 μM= 50% and an IC_{50}= 1.5 μM (enzymatic).

Example 74: Compound 74



1-[3-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-ylamino)-propyl]-pyrrolidin-2-one: Procedure was taken from WO 03/051366, Example 386A. Purified by preparatory TLC MeOH/CH_2Cl_2 (4:96). Isolated yield is 25%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J= 3 Hz, 1H), 7.41 (dd, J= 3.9 1.2 Hz, 1H), 7.35 (dd, J= 4.2, 0.9 Hz, 1H), 7.20 (dd, J= 2.7, 0.9 Hz, 1H), 7.14 (dd, J= 2.7, 0.9 Hz, 1H), 7.05 (d, J= 3 Hz, 1H), 6.97 (dd, J= 3.9, 1.2 Hz, 1H), 6.91 (dd, J= 3.6, 1.2 Hz, 1H), 5.72 (t, J= 6 Hz, 1H) 3.36-3.29 (m, 4H), 3.22 (d, J= 6 Hz, 2H), 2.38 (t, J= 7.8 Hz, 2H), 2.01-1.90 (m, 2H), 1.83 (p, J= 6.6, 6 Hz, 2H). ESI MS: 436 (M+1). The assay data yielded PI @ 11.1μM= 34% and an Enzymatic IC_{50} = 25 μM.

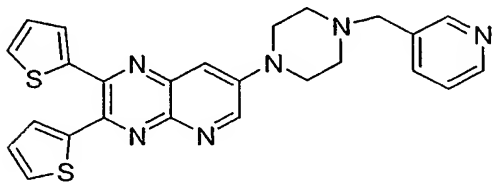
Example 75: Compound 75



4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (0.52 mmol, 200 mg) was dissolved in trifluoroacetic acid (5 ml) and stirred at room temperature for 30 mins, The crude mixture was concentrated, dissolved in water,

and washed with diethylether (3 x 10 ml). The aqueous layer was then basified to pH 10 and extracted with CH_2Cl_2 (3 x 10 ml). The combined layers were dried with Na_2SO_4, filtered, and concentrated, affording 7-Piperazin-1-yl-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine (44% Yield). ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.30 (d, J= 3.0 Hz, 1H), 8.39 (d, J= 3.3 Hz, 1H). 7.90-7.88 (m, 2H), 7.57 (dd, J= 2.7, 0.9 Hz, 2H), 7.29-7.22 (m, 2H), 4.01 (t, J= 6Hz, 4H), 3.67 (t, J= 6.0 Hz, 4H). ESI MS: 380 (M+1). The assay data yielded PI@ 10 μM = 45% and an Enzymatic IC_{50} = 4.5 μM.

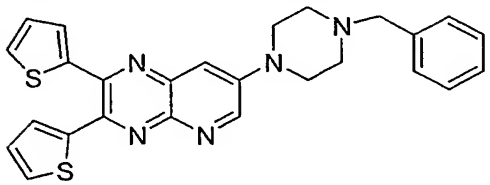
Example 76: Compound 76



7-Piperazin-1-yl-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine (0.10 mmol, 40 mg), aldehhyde (0.11 mmol), sodium triacetoxy borohydride (0.21 mmol, 44 mg), and glacial acetic acid (3 L, 0.05 mmol, 3.1 mg) were dissolved in CH_2Cl_2 and left to stir overnight at room temperature. The solution was then diluted with CH_2Cl_2 (10 ml), washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude material was then purified as described in following examples.

7-(4-Pyridin-3-ylmethyl-piperazin-1-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine: Purified with preparatory TLC (1:1 Hexane/EtOAc). Isolated yield is 67%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J= 3 Hz, 1H), 8.52 (d, J= 1.8 Hz, 1H), 8.48 (dd, J= 2.4, 1.5 Hz, 1H), 7.66 (dt, J= 6, 3 Hz, 1H), 7.44-7.38 (m, 3H), 7.25-7.18 (m, 3H), 6.99 (dd, J= 6, 1.5 Hz, 1H), 6.93 (dd, J= 1.2, 3 Hz, 1H), 3.54 (s, 2H), 3.42 (t, J = 9.0 Hz, 4H), 2.63 (t, J= 6 Hz, 4H). ESI MS: 471 (M+1). The assay data yielded PI@ 10 μM = 37%, Enzymatic IC_{50}= 8.6 μM and a CB IC_{50} = 27 μM.

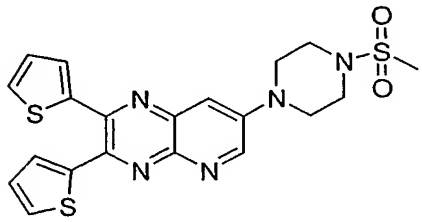
Example 77: Compound 77



7-(4-Benzymaticyl-piperazin-1-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine: Purified with preparatory TLC (3:7 EtOAc/Hexane). Isolated yield is 26%. ^{1}H-NMR (300 MHz,

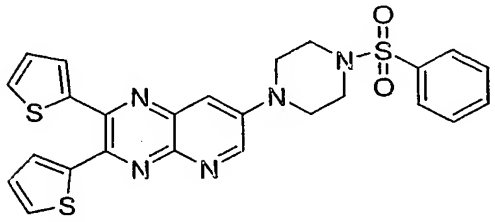
$CDCl_3$) δ 8.89 (d, 3 Hz, 1H), 7.44-7.38 (m,3H), 7.30-7.28 (m,3H), 7.24 (dd, J= 3, 0.9 Hz, 2H), 7.20 (dd, J= 1.8, 0.9 Hz, 2H), 6.99 (dd, J= 3.6, 1.5 Hz, 1H), 6.94 (dd, J= 1.8, 0.9 Hz, 1H), 3.56 (s, 2H), 3.41 (d, J= 6 Hz, 4H), 2.63 (s, 4H). ESI MS: 470 (M+1). The assay data yielded PI @ 10 M = 49%, Enzymatic IC_{50} = 0.9 μM and an CB IC_{50} = 3 μM.

Example 78: Compound 78



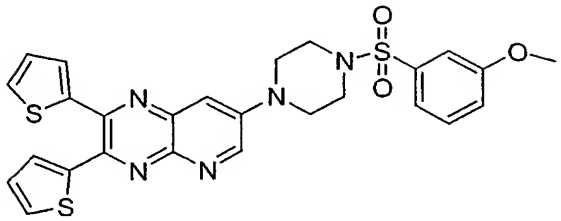
7-Piperazin-1-yl-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine (0.10 mmol, 40 mg), sulfonyl chloride (0.14 mmol), and triethylamine (19 L, 0.14 mmol, 14 mg) were dissolved in CH_2Cl_2 and left to stir overnight at room temperature. The solution was then diluted with CH_2Cl_2 (10 ml), washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude material was purified as described in the following examples. 7-(4-Methanesulfonyl-piperazin-1-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine: Purified by preparatory TLC (1:19 MeOH/ CH_2Cl_2). Isolated yield is 36%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J= 3, 1H), 7.51 (d, J= 3 Hz, 1H), 7.47 (dd, J= 6, 0.9 Hz, 1H), 7.43 (dd, J= 3, 0.9 Hz, 1H), 7.28-7.24 (m, 2H), 7.02 (dd, J= 6, 1.2 Hz, 1H), 6.96 (dd, J= 6, 1.2 Hz, 1H), 3.51 (m, 4H), 3.43 (m, 4H), 2.80 (s, 3H). ESI MS: 458 (M+1). The assay data yielded PI @ 10 μM = 76% and an Enzymatic IC_{50} = 2.7 μM.

Example 79: Compound 79



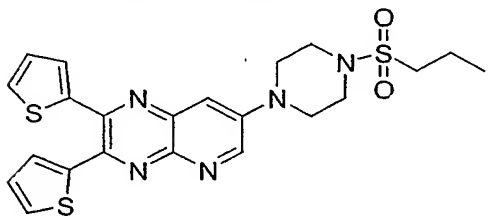
7-(4-Benzymaticenesulfonyl-piperazin-1-yl)-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine: Purified by preparatory TLC (13:7 Hexane/EtOAc). Isolated yield is 47%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J= 3 Hz, 1H), 7.75 (d, J= 6 Hz, 2H), 7.75-7.48 (m, 3H), 7.45-7.39 (m, 3H), 7.24 (d, J= 3 Hz, 1H), 7.21 (J= 3 Hz, 1H), 6.99 (t, J= 6 Hz, 1H), 6.94 (t, J= 6 Hz, 1H), 3.46 (t, J= 3 Hz, 4H), 3.21 (t, J= 6 Hz, 4H). LCMS: 520 (M+1). The assay data yielded PI @ 11.1 μM = 43% and an Enzymatic IC_{50} = 8.8 μM.

Example 80: Compound 80



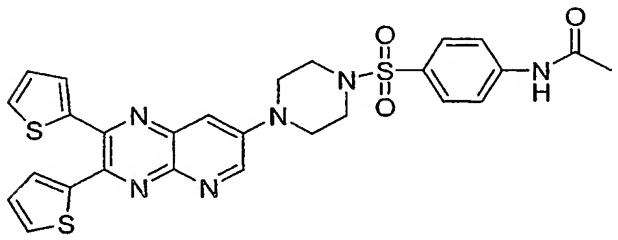
7-[4-(3-Methoxy-benzymaticenesulfonyl)-piperazin-1-yl]-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine: Purified by preparatory TLC (1:4 EtOAc/Hexane). Isolated yield is 70%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J= 3 Hz, 1H), 7.45-7.38 (m, 4H), 7.32 (dt, J= 6, 3 Hz, 1H), 7.25-7.19 (m, 3H), 7.09 (ddd, J= 4.8, 1.5, 0.9 Hz, 1H), 6.96 (dd, J= 3.9, 3Hz, 1H), 6.94 (dd, J= 6, 1.2 Hz, 1H), 3.80 (s, 3H), 3.46 (t, J= 4.8 Hz, 4H), 3.21 (t, J= 5.1 Hz, 4H). LCMS: 550 (M+1). The assay data yielded PI @ 11.1μM= 67% and an Enzymatic IC_{50} = 1.2 μM.

Example 81: Compound 81



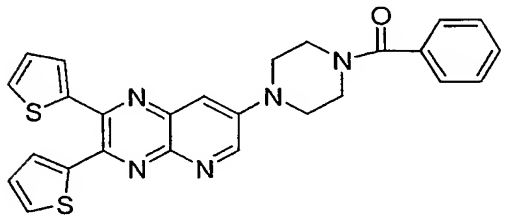
7-[4-(Propane-1-sulfonyl)-piperazin-1-yl]-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine: Purified by preparatory TLC (1:4 MeOH/CH_2Cl_2). Isolated yield is 31%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J= 3 Hz, 1H), 7.50 (d, J= 3 Hz, 1H), 7.47 (dd, J= 3.9, 1.2 Hz, 1H), 7.43 (dd, J= 4.2, 0.9 Hz, 1H), 7.27 (dd, J= 2.4, 1.2 Hz, 1H), 7.25 (dd, J= 3, 0.9 Hz, 1H), 7.00 (dd, J= 1.2, 3.9 Hz, 1H), 6.95 (dd, J= 1.2, 3 Hz, 1H), 3.46 (s, 8H), 2.91-2.86 (m, 2H), 1.87-1.80 (m, 2H), 1.15-1.00 (m, 3H). ESI MS: 486 (M+1). The assay data yielded PI @ 11.1 μM= 68%, Enzymatic IC_{50} = 2.4 μM and an CB IC_{50} = 8.36 μM.

Example 82: Compound 82



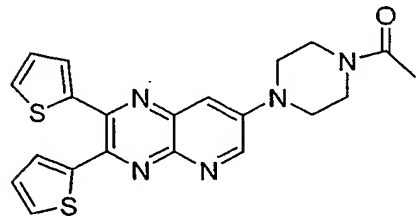
N-{4-[4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazine-1-sulfonyl]-phenyl}-acetamide: Purified by preparatory TLC (3:7 MeOH/ CH_2Cl_2). Isolated yield is 57%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J= 2.7 Hz, 1H), 7.84 (s, 1H), 7.66 (s, 4H), 7.46-7.40 (m, 3H), 7.26 (dd, J= 2.7, 0.9 Hz, 1H), 7.22 (dd, J= 3.0, 0.9 Hz, 1H), 6.99 (dd, J= 3, 1.2 Hz, 1H), 6.94 (dd, J= 3, 1.2 Hz, 1H), 3.46 (t, J= 4.5 Hz, 4H), 3.17 (t, J= 3 Hz, 4H), 2.14 (s, 3H). ESI MS: 577 (M+1). The assay data yielded PI @ 11.1 μM= 41% and an Enzymatic IC_{50} = 28 μM.

Example 83: Compound 83



7-Piperazin-1-yl-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine (0.11 mmol, 40 mg), triethylamine (19μM, 0.14 mmol, 14 mg), and acetyl chloride (15 μL, 0.14 mmol, 19 mg) were dissolved in CH_2Cl_2 and left to stir at room temperature overnight. The solution was then diluted with CH_2Cl_2 (10ml), washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude material was purified as described in the following examples. [4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-phenyl-methanone: Purified by preparatory TLC (1:4 Hexane/EtOAc). Isolated yield is 80%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.91 (d, J= 3.0 Hz, 1H), 7.51 (d, J= 3 Hz, 1H), 7.47 (dd, J= 2.1, 1.2 Hz, 1H), 7.43 (dd, J= 3.9, 0.9 Hz, 1H), 7.40-7.37 (m, 5H), 7.28 (dd, J= 2.7, 0.9 Hz, 1H), 7.25 (dd, J= 1.8, 1.2 Hz, 1H), 7.01 (dd, J= 3.6, 1.5 Hz, 1H), 6.95 (dd, J= 3.9, 1.5, 1H), 3.83 (br s, 4H), 3.41 (br s, 4H).- ESI MS:- 484 (M+1). The assay data yielded PI@ 10 μM = 90% and an enzymatic IC_{50} = 2.3 μM.

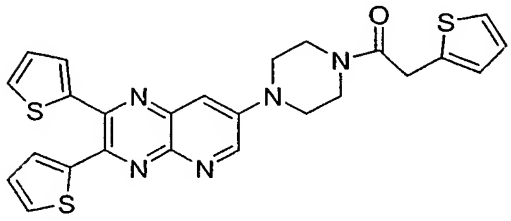
Example 84: Compound 84



1-[4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-ethanone: (Note: acetic anhydride was used as acylating agent). Purified by preparatory TLC (1:19

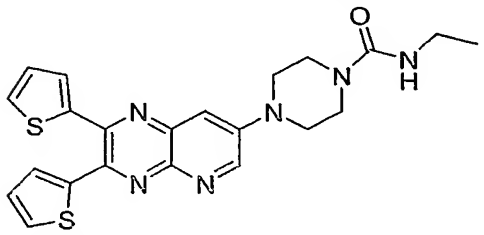
MeOH/CH_2Cl_2). Isolated yield is 22% (7.3 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J= 3 Hz, 1H), 7.47-7.44 (m, 2H) 7.41 (dd, J= 6, 0.6 Hz, 1H), 7.27 (dd, J= 2.7, 0.9 Hz, 1H), 7.23 (dd, J= 2.7, 0.9, 1H), 7.00 (dd, J= 3, 1.3 Hz, 1H), 6.95 (dd, J= 3, 1.3 Hz, 1H), 3.89 (t, J= 6 Hz, 2H), 3.67 (t, J= 3 Hz, 2H), 3.42-3.34 (m, 4H), 2.11 (s, 3H). ESI MS: 422 (M+1). The assay data yielded PI @ 10μM= 63% and an Enzymatic IC_{50} = 13 μM.

Example 85: Compound 85



1-[4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-2-thiophen-2-yl-ethanone: Purified by preparatory TLC (1:4) Hexane/EtOAc). Isolated yield is 55% (40 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.86 (d, J= 3.0 Hz, 1H), 7.48 (dd, J= 6.0, 3.0 Hz, 1H), 7.41 (d, J= 3.0 Hz, 2H), 7.25 (dd, J= 3.0, 0.9 Hz, 1H), 7.22 (dd, J= 3.0, 0.9, 1H), 7.16 (dd, J= 3.6, 1.5 Hz, 1H), 6.99 (dd, J= 3.0, 1.2 hz, 1H), 6.94-6.86 (m, 3H), 3.91 (s, 2H), 3.83 (t, J= 5.1 Hz, 2H), 3.70 (t, J= 4.5 Hz, 2H), 3.36 (t, J= 5.1 Hz, 2H), 3.25 (t, 4.8 Hz, 2H). ESI MS: 504 (M+1). The assay data yielded PI @ 11.1μM= 77%, Enzymatic IC_{50} = 1.2 μM and a CB IC_{50} = 1.6 μM.

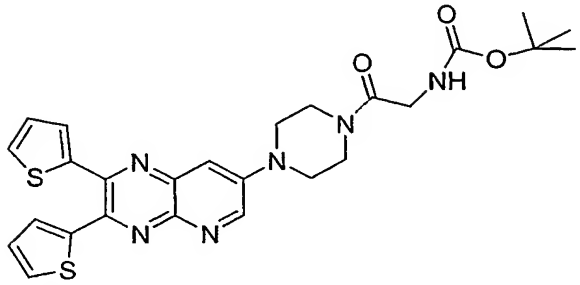
Example 86: Compound 86



7-Piperazin-1-yl-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine (0.13 mmol, 50mg) and ethyl isocyanate (20.8 l, 0.26 mmol, 18.7 mg) were dissolved in CH_2Cl_2 at 0°C. The solution was left to stir overnight at room temperature. The product, 4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazine-1-carboxylic acid ethylamide, was isolated from the crude reaction mixture by filtration and did not require further purification. Isolated yield is 25% (15 mg). ^{1}HNMR (300 MHz, DMSO-d_6) δ 9.15 (d, J=3 Hz, 1H), 7.81 (ddd, J= 3.9, 1.8, 0.9, 2H), 7.56 (d, J= 3, 1H), 7.23-7.09 (m, 4H), 6.64 (br s, 1H),

3.32 (s, 8H), 3.10 (p, J= 5.2, 2H), 1.03 (t, J= 2.7 Hz, 3H). ESI MS: 415 (M+1). The assay data yielded PI @ 11.1 μM= 43%, Enzymatic IC_{50} = 16 μM and a CB IC_{50} = 0.4 μM.

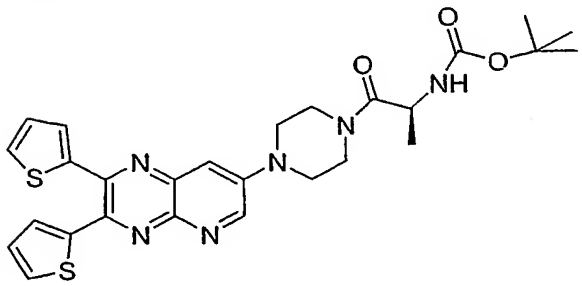
Example 87: Compound 87



7-Piperazin-1-yl-2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazine (0.09 mmol, 40 mg), 1-hydroxybenzymaticotriazole hydrate (0.12 mmol, 15.6 mg), 1-(3-dimethylaminopropyl)-3-ethylcarboxiimide hydrochloride (0.12 mmol, 22.1 mg), triethylamine (37 L, 0.27 mmol, 26.9 mg), and (*L*)-Boc-amino acid (0.12 mmol) were dissolved in CH_2Cl_2 and left to stir overnight at room temperature. The solution was diluted with CH_2Cl_2 (10 ml), washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude material was purified as described in the following examples.

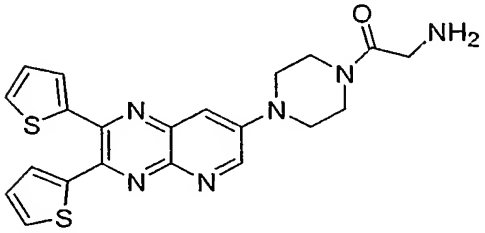
{2-[4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester: Purified by preparatory TLC (3:97) MeOH/CH_2Cl_2). Isolated yield is 50% (64 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J= 3 Hz, 1H), 7.47 (m, 2H), 7.43 (dd, J= 3.9, 1.2 Hz, 1H), 7.27 (dd, J= 3.9, 0.9 Hz, 2H) 7.00 (dd, J= 3.9, 1.2 Hz, 1H), 6.95 (dd, J= 3.6, 1.2 Hz, 1H), 5.42 (br s, 1H), 3.98 (d, J= 3.9 Hz, 2H), 3.82 (br s, 2H), 3.60 (br s, 2H), 3.40 (d, J= 3.9 Hz, 4H), 1.39 (s, 9H). ESI MS: 537 (M+1). The assay data yielded PI @ 11.1 μM= 79 % and an Enzymatic IC_{50} = 1.9 μM.

Example 88: Compound 88



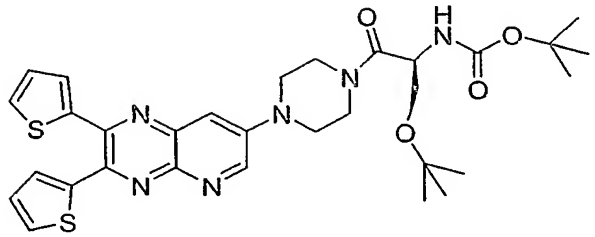
{2-[4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-1-methyl-2-oxo-ethyl}-carbamic acid tert-butyl ester: Purified by preparatory TLC (3:97 MeOH/CH_2Cl_2). Isolated yield is 50% (85 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J= 3 Hz, 1H), 7.45-7.39 (m, 3H), 7.25 (dd, J= 6, 3.6, 2H), 6.99 (dd, J= 4.8, 4.5 Hz, 1H), 6.94 (dd, J= 5.1, 4.5 Hz, 1H), 5.42 (d, J= 8.1 Hz, 1H), 4.66 (p, J= 7.2 Hz, 1H), 3.91-3.62 (m, 4H), 3.40 (s, 4H), 1.37 (s, 9H), 1.29 (J= 6.6 Hz, 3H). ESI MS: 551 (M+1). The assay data yielded PI @ 11.1 μM= 78% and an Enzymatic IC_{50} = 1.7 μM.

Example 89: Compound 89



2-Amino-1-[4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-ethanone: Into a solution of MeOH (3 ml) at 0°C, acetyl chloride (1 ml) was added and was allowed to stir for 15 mins. {2-[4-(2,3-Di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (0.12 mmol, 64 mg) was then dissolved in this solution and was stirred for 30 mins. The mixture and was subsequently triturated with ether, affording the title product. Isolated yield is 69% (36 mg). ^{1}H-NMR (300 MHz, Methanol-d_4) δ 9.01 (d, J= 3 Hz, 1H), 8.13 (d, J= 3 Hz, 1H), 7.65-7.63 (m, 2H), 7.33-7.30 (m, 2H), 7.00-6.96 (m, 2H), 4.78 (br s, 2H), 3.92 (s, 2H), 3.77 (t, J= 4.5 Hz, 2H), 3.60-3.53 (m, 6H). ESI MS: 436 (M+1). The assay data yielded PI @ 11.1 μM= 54% and an Enzymatic IC_{50} = 24 μM.

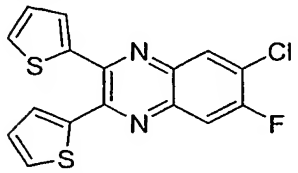
Example 90: Compound 90



{1-tert-Butoxymethyl-2-[4-(2,3-di-thiophen-2-yl-pyrido[2,3-b]pyrazin-7-yl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester: Purified by preparatory TLC (4:96) MeOH/CH_2Cl_2). Isolated yield is 50% (98 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.89 (d,

J= 3 Hz, 1H), 7.45-7.39 (m, 3H), 7.25 (dd, J= 2.7, 0.9 Hz, 1H), 7.21 (dd, J= 2.7, 0.9 Hz, 1H), 6.99-6.96 (m, 1H), 6.94-6.91 (m, 1H), 5.37 (d, J= 8.1 Hz, 1H), 4.78 (m, 1H), 3.86-3.78 (m, 4H), 3.54-3.33 (m, 6H), 1.37 (s, 9H), 1.08 (s, 9H). ESI MS: 632 (M+1). The assay data yielded PI @ 11.1 μM= 80% and an Enzymatic IC_{50} = 0.8 μM.

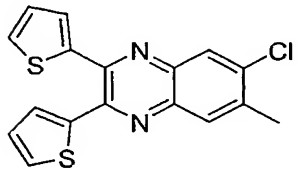
Example 91: Compound 91



A solution of 2,2'-Thenil (0.31 mmol, 69 mg), substituted phenylene diamine (0.31 mmol), and a catalytic amount of Toluene-4-sulfonic acid in MeOH (5 ml) was stirred at room temperature overnight. MeOH was concentrated and the residue was diluted with CH_2Cl_2 (10 ml), washed with water, dried with Na_2SO_4, and concentrated. The crude material was recrystalized in MeOH.

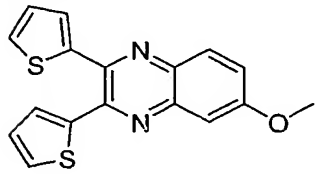
6-Chloro-7-fluoro-2,3-di-thiophen-2-yl-quinoxaline: Isolated yield is 75% (81 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J= 6.6, 1.2 Hz, 1H), 7.68 (dd, J= 8.1, 1.2 Hz, 1H), 7.42-7.39 (m, 2H), 7.17-7.15 (m, 2H), 6.95-6.92 (m, 2H). ESI MS: 347 (M+1). The assay data yielded PI @ 10 μM = 31% and an Enzymatic IC_{50} = 59 μM.

Example 92: Compound 92



6-Chloro-7-methyl-2,3-di-thiophen-2-yl-quinoxaline: Isolated yield is 73% (78 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.74 (d, J= 0.6 Hz, 1H), 7.31 (dd, J= 3.9, 1.2 Hz, 2H), 7.06-7.04 (m, 2H), 6.85-6.82 (m, 2H) 2.40 (d, J= 0.3 Hz, 3H). ESI MS: 343 (M+1). The assay data yielded PI @ 10 μM= 58% and an Enzymatic IC_{50} = 82 μM.

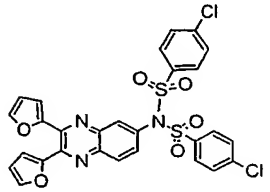
Example 93: Compound 93



6-Methoxy-2,3-di-thiophen-2-yl-quinoxaline: Isolated yield is 37% (28 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 1H), 7.42-7.38 (m, 2H), 7.31-7.29 (m, 2H), 7.14 (dd, J= 2.7, 0.9 Hz, 2H), 6.98-6.95 (m, 2H), 3.90 (s, 3H). ESI MS: 325 (M+1). The assay data yielded PI @ 10μM = 59%, Enzymatic IC_{50} = 45 μM and a CB IC_{50} = 0.44 μM.

Example 94: Compound 94

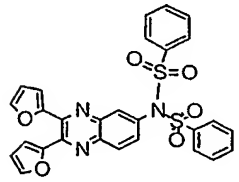
Typical Procedure for Bis-Quinoxaline-sulfonamide series:



A mixture of 2,3-di(2-furyl)-6-quinoxalinylamine (0.4 mmol, 111 mg), 4-chloro-benzymaticenesulfonyl chloride (1.0 mmol, 210 mg), triethyl amine (1.2 mmol, 121 mg) and 4-*N*, *N*-dimethylaminopyridine (DMAP, 0.12 mmol, 15 mg) in anhydrous CH_2Cl_2 (10 ml) was stirred at 65 °C overnight. After cooling, CH_2Cl_2 (30 ml) was added. The organic phase was washed with saturated $NaHCO_3$ (aq), water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography (silica gel) with Hexanes/EtOAc (8:1 to 2:1) as an eluent to give 4-chloro-*N*-(4-chlorophenylsulfonyl)-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide.

4-Chloro-*N*-(4-chlorophenylsulfonyl)-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: Isolated yield is 64% (160 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 1H), 7.92–7.88 (m, 5H), 7.66–7.64 (m, 2H), 7.57–7.54 (m, 4H), 7.33 (dd, J = 9.0, 2.4 Hz, 1H), 6.75–6.73 (m, 2H), 6.60–6.58 (m, 2H). ESI MS: 626 (*M*+1). The assay data yielded PI @ 25 μM = 87% and an IC_{50} = 3.5 μM.

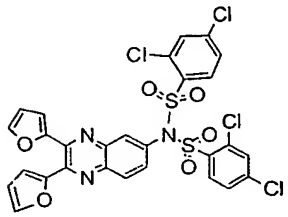
Example 95: Compound 95



N-(Phenylsulfonyl)-*N*-(2,3-di(2-furyl)-6-quinoxalinyl)benzymaticenesulfonamide: For a representative procedure, see example 93. Isolated yield is 77% (170 mg). ^{1}H-NMR

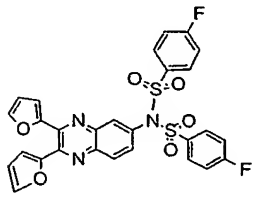
(300 MHz, $CDCl_3$) δ 8.08 (d, J = 9.0 Hz, 1H), 7.98–7.92 (m, 5H), 7.73–7.63 (m, 4H), 7.59–7.54 (m, 4H), 7.33 (dd, J = 9.0, 2.4 Hz, 1H), 6.72 (dd, J = 3.3, 0.6 Hz, 2H), 6.58 (dd, J = 3.3, 1.8 Hz, 2H). ESI MS: 558 (M+1). The assay data yielded PI @ 25 μM = 78% and an IC_{50} = 17 μM.

Example 96: Compound 96



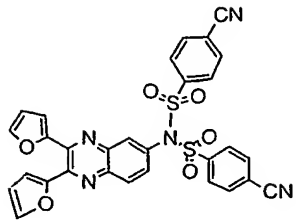
2,4-Dichloro-*N*-(2,4-dichlorophenylsulfonyl)-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: For a representative procedure, see example 103. Isolated yield is 60% (166 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18–8.09 (m, 4H), 7.71 (dd, J = 9.0, 2.4 Hz, 1H), 7.65 (s, 2H), 7.52 (s, 1H), 7.51 (s, 1H), 7.42 (dd, J = 8.7, 2.1 Hz, 2H), 6.75–6.73 (m, 2H), 6.60–6.58 (m, 2H). ESI MS: 696 (M+1). The assay data yielded PI @ 10 μM = 73%.

Example 97: Compound 97



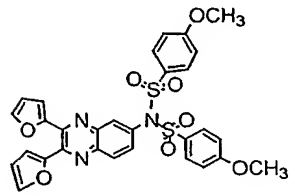
4-Fluoro-*N*-(4-fluorophenylsulfonyl)-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: For a representative procedure, see example 93. Isolated yield is 74% (176 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 1H), 8.03–7.96 (m, 4H), 7.90 (d, J = 2.4 Hz, 1H), 7.64 (dd, J = 3.6, 1.2 Hz, 2H), 7.32 (dd, J = 9.0, 2.4 Hz, 1H), 7.28–7.21 (m, 4H), 6.74–6.73 (m, 2H), 6.59 (dd, J = 3.3,1.8 Hz, 2H). ESI MS: 594 (M+1). The assay data yielded PI @ 10 μM = 52%.

Example 98: Compound 98



4-Cyano-*N*-(4-cyanophenylsulfonyl)-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: For a representative procedure, see example 93. Isolated yield is 58% (141 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 8.7 Hz, 4H), 7.90 (d, J = 8.7 Hz, 4H), 7.88–7.87 (m, 1H), 7.67–7.65 (m, 2H), 7.30 (dd, J = 9.0, 2.4 Hz, 1H), 6.77 (dd, J = 8.7, 3.6 Hz, 2H), 6.62–6.59 (m, 2H). ESI MS: 608 (M+1). The assay data yielded PI @ 10 μM = 58%.

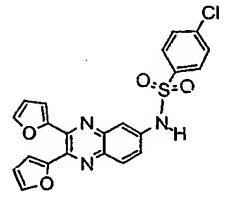
Example 99: Compound 99



4-Methoxy-*N*-(4-methoxyphenylsulfonyl)-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: For a representative procedure, see example 93. Isolated yield is 70% (173 mg). ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.07 (d, J = 8.7 Hz, 1H), 7.93–7.86 (m, 5H), 7.65–7.63 (m, 2H), 7.35 (dd, J = 8.7, 2.1 Hz, 1H), 7.03–6.98 (m, 4H), 6.72–6.70 (m, 2H), 6.58 (dd, J = 3.3, 1.8 Hz, 2H), 3.92 (s, 6H). ESI MS: 618 (M+1). The assay data yielded PI @ 10 μM = 58%.

Example 100: Compound 100

Typical Procedure for the preparation of mono-quinoxaline-sulfonamide

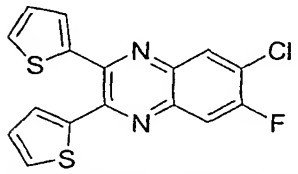


A mixture of 4-chloro-*N*-(4-chlorophenylsulfonyl)-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide (0.2 mmol, 125 mg) and tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.3 mmol, 0.3 ml) in anhydrous THF (8 ml) was stirred at

60 °C for 3 h. Most of THF was removed in vacuo and EtOAc (60 ml) was added. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography (silica gel) with Hexanes/EtOAc (8:1 to 2:1) as an eluent to give 4-chloro-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide.

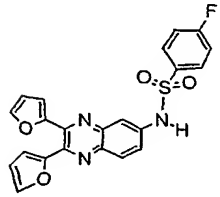
4-Chloro-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: The isolated yield is 69% (62 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 9.0 Hz, 1H), 7.84–7.80 (m, 2H), 7.75 (d, J = 2.4 Hz, 1H), 7.61–7.59 (m, 2H), 7.57 (dd, J = 9.0, 2.4 Hz, 1H), 7.43–7.40 (m, 2H), 7.34 (s, 1H), 6.66–6.64 (m, 2H), 6.55 (dd, J = 3.3, 1.8 Hz, 2H). ESI MS: 452 (M+1). The assay data yielded PI @ 10 μM = 93%.

Example 101: Compound 101



2,4-Dichloro-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: For a representative procedure, see example 99. The isolated yield is 80% (77 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.61–7.58 (m, 4H), 7.49 (d, J = 1.8 Hz, 1H), 7.31 (dd, J = 8.7, 1.8 Hz, 1H), 6.64–6.62 (m, 2H), 6.56–6.54 (m, 2H). ESI MS: 486 (M+1). The assay data yielded PI @ 10 μM = 91%.

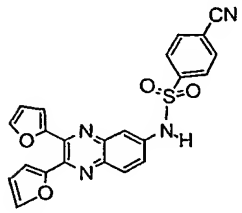
Example 102: Compound 102



4-Fluoro-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: For a representative procedure, see example 99. The isolated yield is 72% (62 mg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 9.0 Hz, 1H), 7.94–7.89 (m, 2H), 7.77 (d, J = 2.4 Hz,

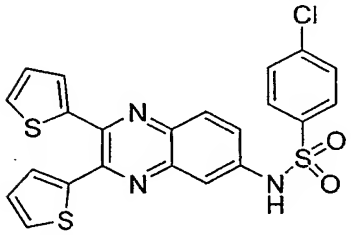
1H), 7.61–7.55 (m, 4H), 7.12 (t, J = 7.5 Hz, 2H), 6.64 (d, J = 2.4 Hz, 2H), 6.55 (dd, J = 3.6,1.8 Hz, 2H). ESI MS: 436 (M+1). The assay data yielded PI @ 10 μM = 84%.

Example 103: Compound 103



4-Cyano-*N*-[2,3-di(2-furyl)-6-quinoxalinyl]benzymaticenesulfonamide: For a representative procedure, see example 99. The isolated yield is 60% (53 mg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 2H), 7.76–7.74 (m, 3H), 7.62–7.60 (m, 2H), 7.56 (dd, J = 9.0, 2.4 Hz, 1H), 7.26 (s, 1H), 6.67 (dd, J = 5.4, 3.6 Hz, 2H), 6.56 (dd, J = 3.3, 1.8 Hz, 2H). ESI MS: 443 (M+1). The assay data yielded PI @ 10 μM = 85%.

Example 104: Compound 104



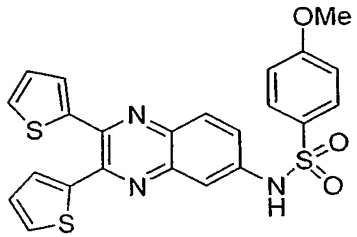
A mixture of 2,3-di-thiophen-2-yl-quinoxalin-6-ylamine (0.3 mmol, 93 mg), 4-chloro-benzymaticenesulfonyl chloride (0.75 mmol, 158 mg), triethyl amine (0.9 mmol, 91 mg) and 4-*N*, *N*-dimethylaminopyridine (DMAP, 0.12 mmol, 15 mg) in anhydrous CH_2Cl_2 (10 ml) was stirred at 65°C overnight. After cooling, CH_2Cl_2 (30 ml) was added. The organic phase was washed with saturated $NaHCO_3$ (aq), water and brine, and dried over anhydrous Na_2SO_4. Removal of solvent in vacuo gave crude 4-chloro-*N*-(4-chlorophenylsulfonyl)-*N*-[2,3- di-thiophen-2-yl-6-quinoxalinyl]benzymaticenesulfonamide.

A mixture of crude 4-chloro-*N*-(4-chlorophenylsulfonyl)-*N*-[2,3- di-thiophen-2-yl-6-quinoxalinyl]benzymaticenesulfonamide and tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.45 mmol, 0.45 ml) in anhydrous THF (8 ml) was stirred at 60 °C for 3 h. Most of THF was removed in vacuo and EtOAc (60 ml) was added. The organic phase was

washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography (silica gel) with Hexanes/EtOAc (8:1 to 2:1) as an eluent to give 4-chloro-*N*-(2,3-di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide.

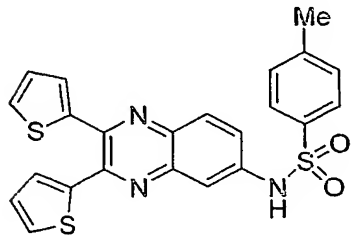
4-Chloro-*N*-(2,3-di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide: For a representative procedure, see example 103. The isolated yield is 48% (69 mg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 9.0 Hz, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.55–7.48 (m, 3H), 7.42 (d, J = 8.7 Hz, 2H), 7.24-7.22 (m, 2H), 7.04-7.01 (m, 2H), 6.85 (s, 1H). ESI MS: 484 (M+1). The assay data yielded PI = 32% @ 10 μM.

Example 105: Compound 105



4-Methoxy-*N*-(2,3-di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide: For a representative procedure, see example 103. The isolated yield is 60% (86 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 2.4 Hz, 1H), 7.56 (dd, J = 9.0, 2.4 Hz, 1H), 7.50-7.46 (m, 2H), 7.22-7.19 (m, 2H), 7.04-7.01 (m, 2H), 6.96-6.93 (m, 1H), 6.89 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H). ESI MS: 480 (M+1). The assay data yielded PI = 29% @ 10 μM.

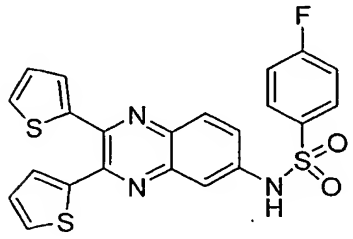
Example 106: Compound 106



4-Methyl-*N*-(2,3-di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide: For a representative procedure, see example 103. The isolated yield is 52% (72 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 9.0, 2.4 Hz, 1H), 7.52-7.49 (m, 2H), 7.28-7.22 (m, 5H), 7.04 (t, J =

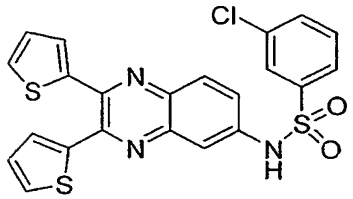
4.5 Hz, 2H), 2.37 (s, 3H). ESI MS: 464 (M+1). The assay data yielded PI = 30% @ 10 μM.

Example 107: Compound 107



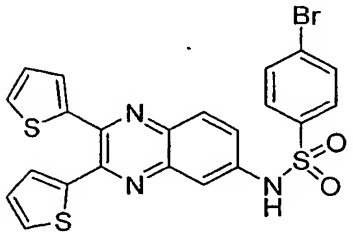
4-Fluoro-*N*-(2,3-di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide: For a representative procedure, see example 103. The isolated yield is 51% (71 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 9.0 Hz, 1H), 7.91-7.86 (m, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.0, 2.4 Hz, 1H), 7.51-7.48 (m, 2H), 7.24-7.21 (m, 2H), 7.16-7.09 (m, 3H), 7.04-7.01 (m, 2H). ESI MS: 468 (M+1). The assay data yielded PI = 33% @ 10 μM.

Example 108: Compound 108



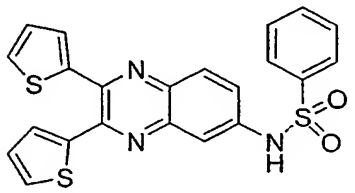
3-Chloro-*N*-(2,3-di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide: For a representative procedure, see example 103. The isolated yield is 61% (88 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 9.0 Hz, 1H), 7.88 (s, 1H), 7.74-7.68 (m, 2H), 7.57-7.48 (m, 4H), 7.39 (t, J = 7.8 Hz, 1H), 7.24-7.21 (m, 2H), 7.03 (t, J = 4.2 Hz, 2H), 6.89 (s, 1H). ESI MS: 484 (M+1). The assay data yielded PI = 35% @ 10 μM.

Example 109: Compound 109



4-Bromo-*N*-(2,3-di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide: For a representative procedure, see example 103. The isolated yield is 55% (87 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 9.0 Hz, 1H), 7.74-7.68 (m, 3H), 7.61-7.48 (m, 5H), 7.23 (td, J = 3.2, 1.2 Hz, 2H), 7.04-7.02 (m, 2H), 6.93 (s, 1H). ESI MS: 528 (M+1). The assay data yielded PI = 34% @ 10 μM.

Example 110: Compound 110



N-(2,3-Di-thiophen-2-yl-quinoxalin-6-yl)-benzymaticenesulfonamide: For a representative procedure, see example 103. The isolated yield is 63% (85 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 1H), 7.94-7.87 (m, 2H), 7.69 (d, J = 2.4 Hz, 1H), 7.57-7.43 (m, 6H), 7.23-7.20 (m, 2H), 7.15 (br s, 1H), 7.04-7.00 (m, 2H). ESI MS: 450 (M+1). The assay data yielded PI = 30% @ 10 μM.

Example 111

Typical procedure:

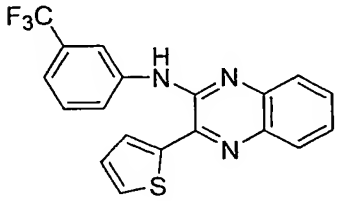
A mixture of benzymaticene-1,2-diamine (50 mmol, 5.41 g) and oxo-thiophen-2-yl-acetic acid ethyl ester (50 mmol, 9.21 g) in EtOH (140 ml) was refluxed for 16 h. The mixture was then immersed into an ice-bath. The precipitate formed was filtered and washed with cold Et_2O to give 3-thiophen-2-yl-1H-quinoxalin-2-one.

3-Thiophen-2-yl-1H-quinoxalin-2-one: The isolated yield is 70% (7.98 g): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.71 (s, 1H), 8.41 (dd, J = 3.9, 1.2 Hz, 1H), 7.84 (dd, J = 5.1, 1.6 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.55-7.50 (m, 1H), 7.37-7.31 (m, 2H), 7.24 (dd, J = 5.1, 3.9 Hz, 1H). ESI MS: 229 (M+1).

A solution of 3-thiophen-2-yl-1H-quinoxalin-2-one (6 mmol, 1.37 g) in $POCl_3$ (60 ml) and DMF (0.5 ml) was stirred at 100°C for 10 h. After cooling, most of $POCl_3$ was removed in vacuo. EtOAc and water were added. The separated organic phase was washed with saturated $NaHCO_3$ (aq), H_2O and brine, and dried over Na_2SO_4. Removal of solvent gave pure 2-chloro-3-thiophen-2-yl-quinoxaline.

2-Chloro-3-thiophen-2-yl-quinoxaline: The isolated yield is 91% (1.34 g): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, J = 3.6, 1.2 Hz, 1H), 8.11-8.07 (m, 1H), 8.01-7.98 (m, 1H), 7.80-7.71 (m, 2H), 7.60 (dd, J = 5.1, 1.2 Hz, 1H), 7.21 (dd, J = 5.1, 3.9 Hz, 1H). ESI MS: 247 (M+1).

Example 112: Compound 112

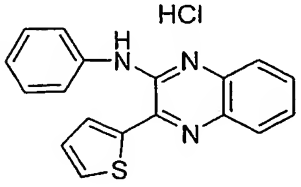


A mixture of 2-chloro-3-thiophen-2-yl-quinoxaline (0.3 mmol, 74 mg) and 3-trifluoromethyl-phenylamine (0.45 mmol, 73 mg) in EtOH (4 ml) was stirred at 140 °C in a sealed tube. After 20 h, most of EtOH was removed in vacuo. EtOAc and water were added. The separated organic phase was washed with saturated $NaHCO_3$ (aq), H_2O, brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography (silica gel) with Hexanes/EtOAc (8:1 to 2:1) as an eluent to give (3-trifluoromethyl-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine.

For the preparation of 2,2-*N,N*-tetramethyl-N'-(3-thiophen-2-yl-quinoxalin-2-yl)-propane-1,3-diamine, 2-morpholin-4-yl-3-thiophen-2-yl-quinoxaline, 2-piperidin-1-yl-3-thiophen-2-yl-quinoxaline, dimethyl-(3-thiophen-2-yl-quinoxalin-2-yl)-amine, and (4-methyl-benzymaticyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine, the reaction temperature used was 100°C.

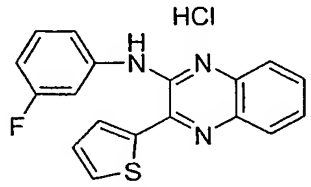
(3-Trifluoromethyl-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: The isolated yield is 70% (78 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.99-7.93 (m, 2H), 7.82 (dd, J = 8.4, 1.2 Hz, 1H), 7.72 (dd, J = 3.6, 0.9 Hz, 1H), 7.66-7.60 (m, 3H), 7.53-7.46 (m, 2H), 7.34 (d, J = 6.4 Hz, 1H), 7.25 (dd, J = 5.1, 3.6 Hz, 1H). ESI MS: 372 (M+1). The assay data yielded PI = 60% @ 10 μM and an IC_{50} = 2.5 μM.

Example 113: Compound 113



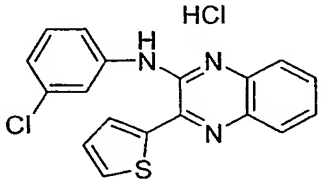
Phenyl-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 68% (62 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.4, 1.2 Hz, 1H), 7.83-7.80 (m, 3H), 7.73 (dd, J = 3.6, 0.9 Hz, 1H), 7.64-7.57 (m, 2H), 7.52 (br s, 1H), 7.46 (td, J = 7.6, 1.5 Hz, 1H), 7.39-7.36 (m, 2H), 7.24 (dd, J = 5.1, 3.6 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H). ESI MS: 304 (M+1). The assay data yielded PI = 85% @ 10 μM and an IC_{50} (cell) = 12 μM.

Example 114: Compound 114



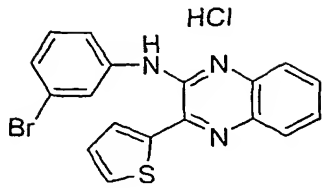
(3-Fluoro-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 65% (63 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01- 7.96(m, 1H), 7.93 (dd, J = 8.4, 1.2 Hz, 1H), 7.85 (dd, J = 8.4, 1.2 Hz, 1H), 7.70 (dd, J = 3.6, 1.2 Hz, 1H), 7.65-7.59 (m, 3H), 7.48 (td, J = 7.6, 1.5 Hz, 1H), 7.30-7.22 (m, 3H), 6.82-6.75 (m, 1H). ESI MS: 322 (M+1). The assay data yielded PI = 83% @ 10 μM and an IC_{50} = 4 μM.

Example 115: Compound 115



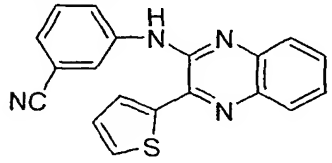
(3-Chloro-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 71% (72 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (t, J = 2.1 Hz, 1H), 7.92 (dd, J = 8.4, 1.2 Hz, 1H), 7.83 (dd, J = 8.4, 1.2 Hz, 1H), 7.69 (dd, J = 3.6, 0.9 Hz, 1H), 7.64-7.58 (m, 3H), 7.51 (br s, 1H), 7.50-7.47 (m, 1H), 7.29-7.22 (m, 2H), 7.07-7.03 (m, 1H). ESI MS: 338 (M+1). The assay data yielded PI = 85% @ 10 μM and an IC_{50} = 4 μM.

Example 116: Compound 116



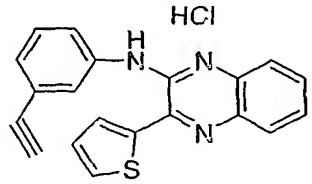
(3-Bromo-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 73% (83 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 3.0, 0.9 Hz, 1H), 7.93 (dd, J = 8.4, 1.2 Hz, 1H), 7.83 (dd, J = 8.4, 1.2 Hz, 1H), 7.71-7.68 (m, 2H), 7.64-7.59 (m, 2H), 7.50 (br s, 1H), 7.48 (td, J = 7.6, 1.2 Hz, 1H), 7.24-7.18 (m, 3H). ESI MS: 382 (M+1). The assay data yielded PI = 84% @ 10 μM and an IC_{50} = 6 μM.

Example 117: Compound 117



3-(3-Thiophen-2-yl-quinoxalin-2-ylamino)-benzymaticonitrile: For a representative procedure, see example 111. The isolated yield is 55% (54 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.40 (t, J = 1.6 Hz, 1H), 7.97 (dd, J = 8.1, 1.2 Hz, 1H), 7.90-7.85 (m, 2H), 7.71 (dd, J = 3.6, 0.9 Hz, 1H), 7.67 (td, J = 6.9, 1.5 Hz, 1H), 7.65 (dd, J = 5.1, 1.2 Hz, 1H), 7.63 (br s, 1H), 7.54 (td, J = 7.6, 1.5 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.37 (dt, J = 7.8, 1.2 Hz, 1H), 7.28 (dd, J = 5.1, 3.6 Hz, 1H). ESI MS: 329 (M+1). The assay data yielded PI = 47% @ 10 μM.

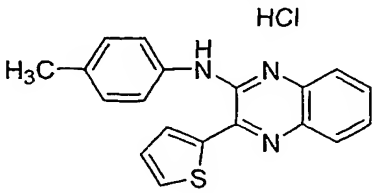
Example 118: Compound 118



(3-Ethynyl-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 52% (51 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.1, 1.2 Hz, 1H), 7.90 (d, J = 1.2 Hz, 1H), 7.90-7.87 (m, 1H), 7.83 (dd, J = 8.4, 1.2 Hz, 1H), 7.71 (dd, J = 3.6, 1.2 Hz, 1H), 7.64-7.58 (m, 2H), 7.51 (br s, 1H), 7.48 (td, J = 7.6, 1.5 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.26-7.21 (m, 2H), 3.09 (s,

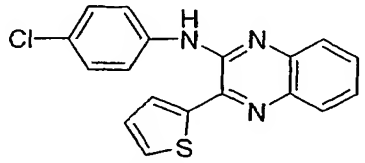
1H). ESI MS: 328 (M+1). The assay data yielded PI = 67% @ 10 μM and an IC_{50} (cell) = 3.1 μM.

Example 119: Compound 119



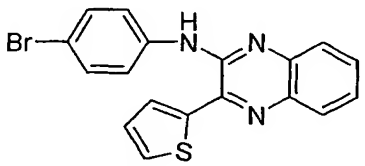
(4-Methyl-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 68% (65 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.1, 1.2 Hz, 1H), 7.79 (dd, J = 8.4, 1.2 Hz, 1H), 7.73 (dd, J = 3.6, 0.9 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.61 (dd, J = 5.1, 0.9 Hz, 1H), 7.58 (td, J = 6.9, 1.5 Hz, 1H), 7.46 (br s, 1H), 7.44 (td, J = 8.4, 1.5 Hz, 1H), 7.23 (dd, J = 5.1, 1.5 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 2.36 (s, 3H). ESI MS: 318 (M+1). The assay data yielded PI = 59% @ 10 μM and an IC_{50} = 4.4 μM.

Example 120: Compound 120



(4-Chloro-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 72% (73 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 8.7 Hz, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 3.6 Hz, 1H), 7.60-7.56 (m, 2H), 7.47 (s, 1H), 7.45 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.20 (t, J = 4.2 Hz, 1H). ESI MS: 338 (M+1). The assay data yielded PI = 63% @ 10 μM and an IC_{50} = 4.4 μM.

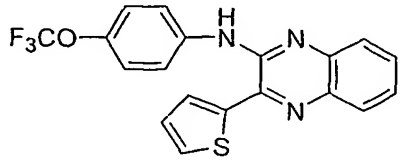
Example 121: Compound 121



(4-Bromo-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 65% (74 mg): ^{1}H-NMR (300 MHz,

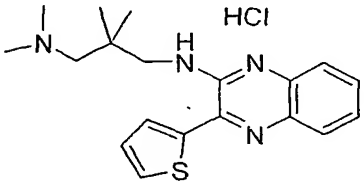
$CDCl_3$) δ 7.93 (dd, J = 8.1, 1.2 Hz, 1H), 7.81 (dd, J = 8.1, 1.2 Hz, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.72-7.70 (m, 1H), 7.63 (td, J = 3.9, 1.2 Hz, 1H), 7.61 (d, J = 6.0, 1.5 Hz, 1H), 7.51-7.46 (m, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.25 (dd, J = 5.1, 3.6 Hz, 1H). ESI MS: 382 (M+1). The assay data yielded PI = 65% @ 10 μM and an IC_{50} = 3.6 μM.

Example 122: Compound 122



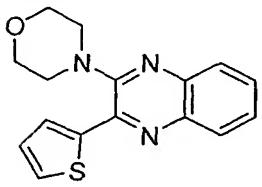
(4-Trifluoromethoxy-phenyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 68% (80 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.1, 1.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.84-7.79 (m, 1H), 7.70 (dd, J = 3.6, 0.9 Hz, 1H), 7.61 (td, J = 5.1, 1.2 Hz, 1H), 7.59 (d, J = 5.4, 1.5 Hz, 1H), 7.53 (br s, 1H), 7.47 (td, J = 7.6, 1.5 Hz, 1H), 7.25-7.21 (m, 3H). ESI MS: 388 (M+1). The assay data yielded PI = 66% @ 10 μM.

Example 123: Compound 123



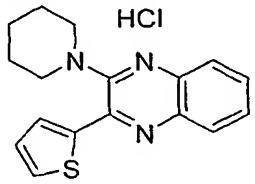
2,2-*N,N*-Tetramethyl-*N'*-(3-thiophen-2-yl-quinoxalin-2-yl)-propane-1,3-diamine: For a representative procedure, see example 111. The isolated yield is 50% (51 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.77 (dd, J = 8.1, 1.2 Hz, 1H), 7.63 (dd, J = 3.6, 0.9 Hz, 1H), 7.59 (dd, J = 8.4, 1.2 Hz, 1H), 7.44-7.39 (m, 2H), 7.25-7.19 (m, 1H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 3.38 (d, J = 4.2 Hz, 2H), 2.19 (s, 2H), 1.95 (s, 6H), 0.96 (s, 6H). ESI MS: 341 (M+1). The assay data yielded PI = 28% @ 10 μM.

Example 124: Compound 124



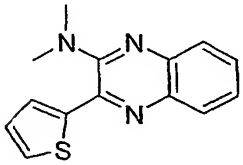
2-Morpholin-4-yl-3-thiophen-2-yl-quinoxaline: For a representative procedure, see example 111. The isolated yield is 72% (64 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, J = 3.6, 1.2 Hz, 1H), 7.96 (dd, J = 8.4, 1.2 Hz, 1H), 7.84 (dd, J = 8.1, 1.2 Hz, 1H), 7.64-7.51 (m, 2H), 7.49 (dd, J = 5.1, 1.2 Hz, 1H), 7.15 (dd, J = 5.1, 3.6 Hz, 1H), 3.91-3.87 (m, 4H), 3.37-3.34 (m, 4H). ESI MS: 298 (M+1). The assay data yielded PI = 52% @ 10 μM.

Example 125: Compound 125



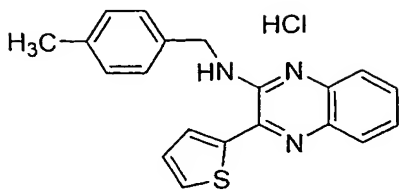
2-Piperidin-1-yl-3-thiophen-2-yl-quinoxaline: For a representative procedure, see example 111. The isolated yield is 66% (58 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J = 3.6, 1.2 Hz, 1H), 7.93 (dd, J = 7.8, 1.2 Hz, 1H), 7.80 (dd, J = 8.1, 1.2 Hz, 1H), 7.59-7.46 (m, 2H), 7.45 (dd, J = 5.1, 0.9 Hz, 1H), 7.13 (dd, J = 5.1, 3.9 Hz, 1H), 3.28-3.24 (m, 4H), 1.78-1.71 (m, 4H), 1.66-1.61 (m, 2H). ESI MS: 296 (M+1). The assay data yielded PI = 75% @ 10 μM and an IC_{50} = 5.1 μM.

Example 126: Compound 126



Dimethyl-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 75% (57 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.80 (dd, J = 8.4, 1.2 Hz, 1H), 7.57 (td, J = 8.1, 1.2 Hz, 1H), 7.51-7.45 (m, 2H), 7.13 (dd, J = 5.1, 3.6 Hz, 1H), 2.95 (s, 6H). ESI MS: 256 (M+1). The assay data yielded PI = 47% @ 10 μM.

Example 127: Compound 127



(4-Methyl-benzymaticyl)-(3-thiophen-2-yl-quinoxalin-2-yl)-amine: For a representative procedure, see example 111. The isolated yield is 60% (60 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.1, 1.2 Hz, 1H), 7.73 (dd, J = 8.1, 1.2 Hz, 1H), 7.63 (dd, J = 3.6, 0.9 Hz, 1H), 7.56 (td, J = 7.5, 1.5 Hz, 1H), 7.50 (dd, J = 5.1, 0.9 Hz, 1H), 7.39 (td, J = 7.6, 1.5 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.13 (dd, J = 5.1, 3.6 Hz, 1H), 5.77 (s, 1H), 4.76 (d, J = 5.4 Hz, 2H), 2.35 (s, 3H). ESI MS: 332 (M+1). The assay data yielded PI = 66% @ 10 μM.

Example 128

Typical Procedure:

A mixture of 4-nitro-benzymaticene-1,2-diamine (30 mmol, 4.59 g) and oxo-thiophen-2-yl-acetic acid ethyl ester (36 mmol, 6.63 g) in EtOH (300 ml) was refluxed in the presence of *p*-toluenesulfonic acid monohydrate (1.8 mmol, 0.34 g) for 24 h. The precipitate formed was filtered directly from hot EtOH solution to give a mixture (5.90 g, yield 72%) of 6-nitro-3-thiophen-2-yl-1H-quinoxalin-2-one and 7-nitro-3-thiophen-2-yl-1H-quinoxalin-2-one with 1.5:1 ratio.

To separate pure 6-nitro-3-thiophen-2-yl-1H-quinoxalin-2-one from the mixture, refluxed 2 g of mixture with EtOH (300 ml) and the solid was collected from hot EtOH solution via filtration. Repeated this procedure two additional times to afford pure 6-nitro-3-thiophen-2-yl-1H-quinoxalin-2-one (0.5 g).

6-Nitro-3-thiophen-2-yl-1H-quinoxalin-2-one: The isolated yield is 18% (1.47 g): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.45 (dd, J = 3.9, 1.2 Hz, 1H), 8.34 (dd, J = 9.0, 2.4 Hz, 1H), 7.94 (dd, J = 4.8, 1.2 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.28 (dd, J = 5.1, 3.9 Hz, 1H). ESI MS: 274 (M+1).

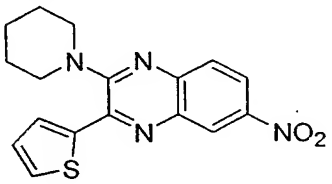
A solution of 6-nitro-3-thiophen-2-yl-1H-quinoxalin-2-one (3.9 mmol, 1.08 g) in $POCl_3$ (80 ml) and DMF (0.5 ml) was stirred at 110 °C for 16 h. After cooling, most of $POCl_3$ was removed in vacuo. The solid was washed with Et_2O, H_2O and Et_2O to give pure 2-chloro-6-nitro-3-thiophen-2-yl-quinoxaline.

2-Chloro-6-nitro-3-thiophen-2-yl-quinoxaline: The isolated yields is 95% (1.08 g): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.86 (d, J = 2.4 Hz, 1H), 8.57 (dd, J = 9.0, 2.4 Hz, 1H), 8.41 (dd, J = 3.9, 1.2 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.07 (dd, J = 5.1, 1.2 Hz, 1H), 7.38 (dd, J = 5.1, 3.9 Hz, 1H). ESI MS: 292 (M+1).

A mixture of 2-chloro-6-nitro-3-thiophen-2-yl-quinoxaline (1 mmol, 0.29 g) and 3-fluoro-phenylamine (2 mmol, 0.22 g) in *i*-PrOH (30 ml) was stirred at 100 °C. After 16 h, the precipitate formed was filtered and washed with small amount of Et_2O to give (3-fluoro-phenyl)-(6-nitro-3-thiophen-2-yl-quinoxalin-2-yl)-amine.

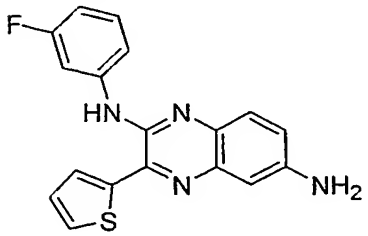
(3-Fluoro-phenyl)-(6-nitro-3-thiophen-2-yl-quinoxalin-2-yl)-amine: The isolated yield is 87% (320 mg); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.70 (d, J = 2.4 Hz, 1H), 8.44 (dd, J = 9.0, 2.4 Hz, 1H), 8.15 (d, J = 3.6 Hz, 1H), 8.06 (d, J = 4.5 Hz, 1H), 7.97-7.92 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.52 (td, J = 8.1, 6.9 Hz, 1H), 7.42 (dd, J = 4.8, 3.9 Hz, 1H), 7.06 (td, J = 8.4, 2.1 Hz, 1H). ESI MS: 367 (M+1).

Example 129



6-Nitro-2-piperidin-1-yl-3-thiophen-2-yl-quinoxaline: For a representative procedure, see example 127. The isolated yield is 90% (310 mg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.74 (d, J = 2.4 Hz, 1H), 8.26 (dd, J = 9.0, 2.4 Hz, 1H), 7.96 (dd, J = 3.9, 1.2 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.46 (dd, J = 5.1, 1.2 Hz, 1H), 7.08 (dd, J = 5.1, 3.9 Hz, 1H), 3.35-3.32 (m, 4H), 1.67-1.63 (m, 6H). ESI MS: 341 (M+1).

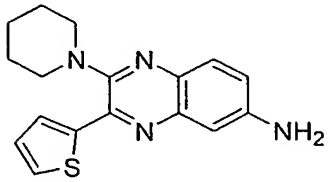
Example 130



A mixture of (3-Fluoro-phenyl)-(6-nitro-3-thiophen-2-yl-quinoxalin-2-yl)-amine (1 mmol, 0.36 g) and Pd/C (50 mg) in dry MeOH (20 ml) was stirred at 40 °C under hydrogen (using a balloon). After 5 h, the reaction mixture was filtered through silica gel, and washed with EtOAc. The combined solution was concentrated in vacuo to give pure 2-*N*-(3-fluoro-phenyl)-3-thiophen-2-yl-quinoxaline-2,6-diamine.

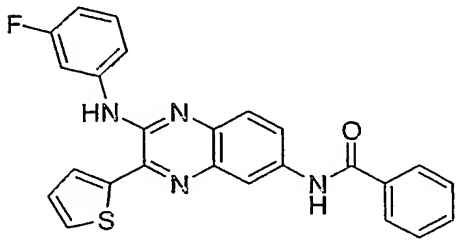
2-*N*-(3-Fluoro-phenyl)-3-thiophen-2-yl-quinoxaline-2,6-diamine: The isolated yield is 89% (300 mg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93-7.87 (m, 1H), 7.71-7.68 (m, 2H), 7.60 (dd, J = 5.1, 0.9 Hz, 1H), 7.35 (br s, 1H), 7.28-7.20 (m, 3H), 7.13-7.08 (m, 2H), 6.77-6.74 (m, 1H), 3.93 (br s, 2H). ESI MS: 337 (M+1).

Example 131



2-Piperidin-1-yl-3-thiophen-2-yl-quinoxalin-6-ylamine: For a representative procedure, see example 129. The isolated yield is 87% (270 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, J = 3.6, 1.2 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.44 (dd, J = 5.1, 1.2 Hz, 1H), 7.14 (dd, J = 5.1, 3.9 Hz, 1H), 7.11 (d, J = 2.7 Hz, 1H), 7.02 (dd, J = 9.0, 2.7 Hz, 1H), 3.94 (br s, 2H), 3.18-3.15 (m, 4H), 1.78-1.71 (m, 4H), 1.65-1.62 (m, 2H). ESI MS: 311 (M+1).

Example 132: Compound 132

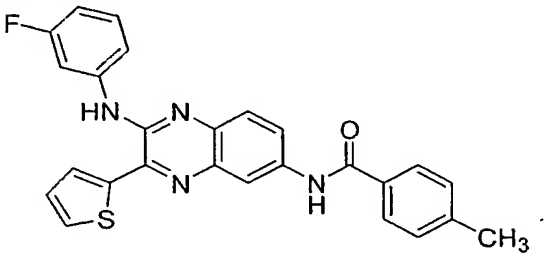


A mixture of 2-*N*-(3-fluoro-phenyl)-3-thiophen-2-yl-quinoxaline-2,6-diamine (0.1 mmol, 34 mg), PhCOCl (0.2 mmol, 28 mg) and Et_3N (0.2 mmol, 20 mg) in dry CH_2Cl_2 (4 ml) was stirred at 25 °C for 16 h. EtOAc and water were added. The separated organic phase was washed with saturated $NaHCO_3$, H_2O, brine, and dried over Na_2S0_4. After removal of solvent in vacuo, the residue was purified by column chromatography (silica gel) with

Hexanes/EtOAc (8:1 to 2:1) as an eluent to give *N*-[2-(3-fluoro-phenylamino)-3-thiophen-2-yl-quinoxalin-6-yl]-benzymaticamide.

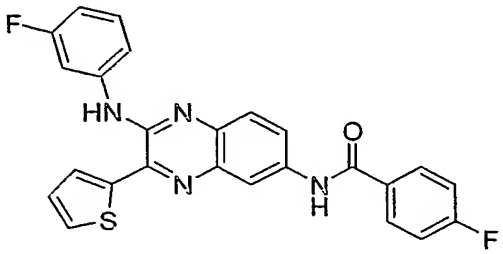
N-[2-(3-Fluoro-phenylamino)-3-thiophen-2-yl-quinoxalin-6-yl]-benzymaticamide: The isolated yield is 70% (31 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 2.4 Hz, 1H), 8.12-8.09 (m, 1H), 8.07 (br s, 1H), 7.98-7.90 (m, 3H), 7.83 (d, J = 9.0 Hz, 1H), 7.73 (dd, J = 3.6, 0.9 Hz, 1H), 7.62 (dd, J = 5.1, 1.2 Hz, 1H), 7.57-7.45 (m, 4H), 7.31-7.24 (m, 3H), 6.82-6.76 (m, 1H). ESI MS: 441 (M+1). The assay data yielded PI = 52% @ 10 μM and an IC_{50} (cell) = 0.1 μM.

Example 133: Compound 133



N-[2-(3-Fluoro-phenylamino)-3-thiophen-2-yl-quinoxalin-6-yl]-4-methyl-benzymaticamide: For a representative procedure, see example 131. The isolated yield is 68% (31 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 2.4 Hz, 1H), 7.99-7.94 (m, 3H), 7.86 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.74 (dd, J = 3.9, 1.2 Hz, 1H), 7.64 (dd, J = 5.1, 1.2 Hz, 1H), 7.57 (br s, 1H), 7.34-7.25 (m, 5H), 6.83-6.77 (m, 1H), 2.45 (s, 3H). ESI MS: 455 (M+1). The assay data yielded PI = 40% @ 10 μM.

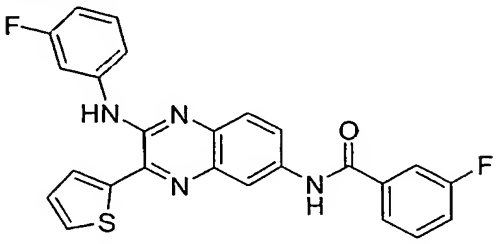
Example 134: Compound 134



N-[2-(3-Fluoro-phenylamino)-3-thiophen-2-yl-quinoxalin-6-yl]-4-fluoro-benzymaticamide: For a representative procedure, see example 131. The isolated yield is 60% (27 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 2.4 Hz, 1H), 7.99-7.81 (m, 6H), 7.72 (d, J = 3.6 Hz, 1H), 7.63 (dd, J = 5.1, 0.9 Hz, 1H), 7.56 (br s, 1H), 7.34-7.15 (m,

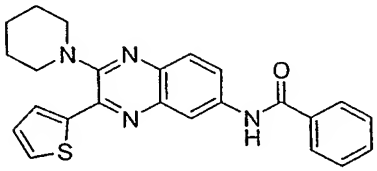
5H), 6.82-6.76 (m, 1H). ESI MS: 459 (M+1). The assay data yielded PI = 36% @ 10 μM and an IC_{50} (cell) = 4.5 μM.

Example 135: Compound 135



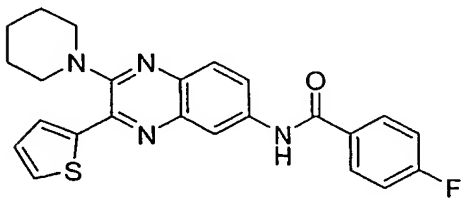
N-[2-(3-Fluoro-phenylamino)-3-thiophen-2-yl-quinoxalin-6-yl]-4-fluoro-benzymaticamide: For a representative procedure, see example 131. The isolated yield is 57% (26 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 2.4 Hz, 1H), 7.99-7.85 (m, 4H), 7.75 (dd, J = 3.6, 0.9 Hz, 1H), 7.69-7.63 (m, 3H), 7.59 (br s, 1H), 7.54-7.47 (m, 1H), 7.33-7.26 (m, 4H), 6.84-6.78 (m, 1H). ESI MS: 459 (M+1). The assay data yielded PI = 34% @ 10 μM.

Example 136: Compound 136



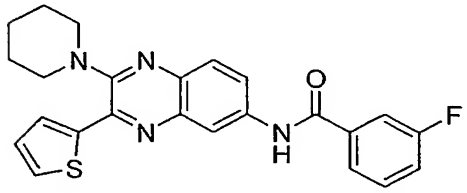
N-(2-Piperidin-1-yl-3-thiophen-2-yl-quinoxalin-6-yl)-benzymaticamide: For a representative procedure, see example 131. The isolated yield is 52% (22 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 3.6, 1.2 Hz, 1H), 7.99 (br s, 1H), 7.89-7.83 (m, 3H), 7.74 (d, J = 9.0 Hz, 1H), 7.52-7.39 (m, 4H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 3.20-3.17 (m, 4H), 1.70-1.67 (m, 4H), 1.60-1.56 (m, 2H). ESI MS: 415 (M+1). The assay data yielded PI = 39% @ 10 μM and an IC_{50} (cell) = 0.29μM.

Example 137: Compound 137



4-Fluoro-*N*-(2-piperidin-1-yl-3-thiophen-2-yl-quinoxalin-6-yl)-benzymaticamide: For a representative procedure, see example 131. The isolated yield is 53% (23 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 2.4 Hz, 1H), 8.08 (dd, J = 3.6, 1.2 Hz, 1H), 8.06 (br s, 1H), 7.85-7.79 (m, 3H), 7.70 (d, J = 9.0 Hz, 1H), 7.39 (dd, J = 5.1, 1.2 Hz, 1H), 7.09-7.03 (m, 3H), 3.19-3.15 (m, 4H), 1.69-1.66 (m, 4H), 1.60-1.56 (m, 2H). ESI MS: 433 (M+1). The assay data yielded PI = 30% @ 10 μM.

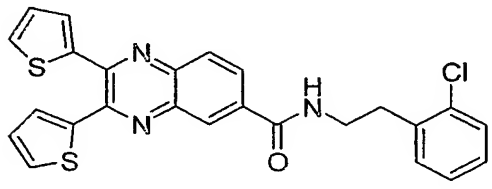
Example 138: Compound 138



3-Fluoro-*N*-(2-piperidin-1-yl-3-thiophen-2-yl-quinoxalin-6-yl)-benzymaticamide: For a representative procedure, see example 131. The isolated yield is 61% (26 mg): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 2.4 Hz, 1H), 8.09 (dd, J = 3.6, 1.2 Hz, 1H), 7.99 (br s, 1H), 7.81 (dd, J = 8.7, 2.1 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.60-7.54 (m, 2H), 7.41-7.36 (m, 2H), 7.22-7.15 (m, 1H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 3.19-3.16 (m, 4H), 1.69-1.66 (m, 4H), 1.60-1.57 (m, 2H). ESI MS: 433 (M+1). The assay data yielded PI = 29% @ 10 μM.

Example 139

General Procedure for 2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(2-chloro-phenyl)-ethyl]-amide.



2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid methyl ester. Methyl-3,4-diaminobenzymaticoate (3.6 g, 16.3 mmol) and 2,2'-thenil (2.5 g, 16.3 mmol) were suspended in ethanol (20 ml). The mixture was heated to reflux and stirred for 16 hours. The crystalline product was collected by filtering the cooled reaction mixture (5.02g, 87%): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.82 (d, J = 2.1 Hz, 1H), 8.34 (dd, J = 8.7, 1.8 Hz,

1H), 8.21 (d, J = 8.7 Hz, 1H), 7.57 (dm, J = 5.1 Hz, 2H), 7.35 (m, 2H), 7.09 (m, 2H), 4.05 (s, 3H). ESI MS: 353 (M+1).

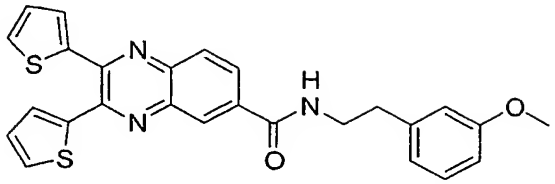
2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid. 2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid methyl ester (2.5 g, 7.10 mmol) was suspended in 60 ml of methanol. To this was added 1.5g (35.5 mmol) of LiOH monohydrate as a solution in 20 ml H_2O and the resulting mixture was warmed to 45°C for 3 hours. Subsequently, the solvents were removed in vacuo. The residue was partitioned between 1N HCl and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to the product as a yellow solid in quantitative yield. ESI MS: 339 (M+1).

2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid N-hydroxysuccinic ester. 2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid (2.4g, 7.1mmol), N-hydroxy succinimide (981 mg, 8.52 mmol), N-hydroxybenzymaticotriazole hydrate (1.15 g, 8.52 mmol) and 4-methylmorpholine (3.9ml, 35.5mmol) were dissolved in 50ml DMF. EDC (2.7g, 14.2 mmol) was added in one portion and the mixture was allowed to stir for 16 hours. The reaction solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and water. The layers were separated, after which the aqueous layer was extracted again with ethyl acetate. The combined organic layers were washed three times with 100 ml water, brine, dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography using 50% ethyl acetate in dichloromethane as the mobile phase (1.38 g, 45%): ESI MS: 436 (M+1).

2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(2-chlorophenyl)-ethyl] amide. In a one dram vial, Succinate ester (30 mg, 0.07 mmol) and (2-chlorophenyl)-ethylamine (19 µL, 0.14 mmol) were dissolved in 3ml dichloromethane and shaken for 16 hours. The reaction mixture was applied directly to a prep TLC plate and eluted with 40% ethyl acetate in hexane (31mg, 95 %). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.90 (t, J = 5.4 Hz, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.08 (dd, J = 8.7, 1.8 Hz, 1H) 7.98 (d, J = 8.7 Hz, 1H), 7.72 (dm, J = 11.0 Hz, 2H), 7.34-7.25 (m, 2H), 7.20-7.11 (m, 4H), 7.03-7.00 (m, 2H), 3.48 (dd, J = 12.9, 7.2 Hz, 2H), 2.92 (t, J = 7.2Hz, 2H). ESI MS: 476 (M+1).

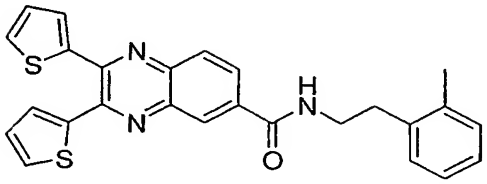
The following compounds were prepared in an analogous manner by using the appropriate aryl-ethylamine instead of (2-chlorophenyl)-ethyl amine.

Example 140: Compound 140



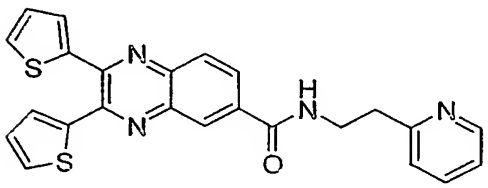
2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(2-methoxyphenyl)ethyl]-amide. Purified by preparatory TLC using 40% ethyl acetate in hexane as eluant (25 mg, 78%): ESI MS: 473 (M+1).

Example 141: Compound 141



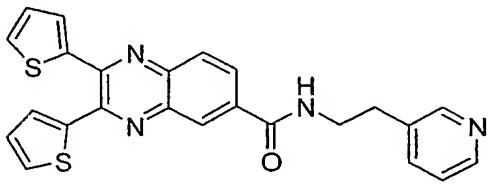
2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(2-tolyl)ethyl]-amide. Purified by preparatory TLC using 40% ethyl acetate in hexane as eluant (25 mg, 80%): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.06 (t, J = 5.6 Hz, 1H), 8.55 (d, J = 1.5Hz, 1H), 8.24 (dd, J = 8.7Hz, 1.8Hz, 1H), 8.12 (d, J = 9 Hz, 1H), 7.85 (ddd, J = 5.7, 1.2, 0.9 Hz, 2H), 7.31 (dd, J = 3.9, 1.2 Hz, 1H), 7.28 (dd, J = 3.9, 1.2 Hz, 1H), 7.23 – 7.10 (m, 5H), 3.56 – 3.49 (m, 2H), 2.90 (t, J = 8.1Hz, 2H), 2.36 (s, 3H). ESI MS: 456 (M+1).

Example 142: Compound 142



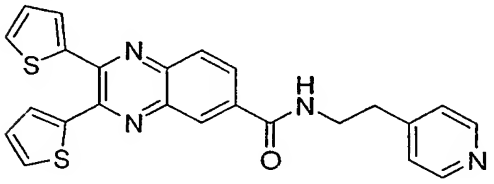
2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(2-pyridyl)ethyl]-amide. Purified by preparatory TLC using 10% methanol in dichloromethane as eluant (20 mg, 66%): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.99 (t, J = 2.4 Hz, 1H), 8.53 (d, J = 2.4 Hz, 2H), 8.21 (dd, J = 8.7, 1.8Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.84 (dt, J = 5.1, 1.5 Hz, 2H), 7.72 (td, J = 7.5, 1.8 Hz 1H), 7.34-7.21 (m, 4H), 7.14 (m, 2H), 3.70 (q, 2H), 3.07 (t, J = 7.5 Hz, 2H). ESI MS: 443 (M+1).

Example 143: Compound 143



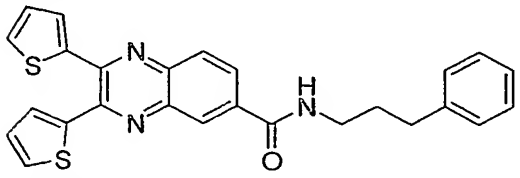
2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(3-pyridyl)ethyl] amide. Purified by preparatory TLC using 10% methanol in dichloromethane as eluant (29 mg, 95%): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.99 (br t, 1H), 8.5 (m, 2H) 8.42 (br d, J = 4.8 Hz, 1H), 8.19 (dd, J = 8.7, 1.8 Hz, 1H), 8.10 (d, J = 8.7Hz, 1H), 7.84 (dt, J = 5.1, 1.5 Hz, 2H), 7.71 (dt, J = 7.8, 1.8 Hz, 1H), 7.35 – 7.26 (m, 3H), 7.14 (m, 2H), 3.60 (dd, J = 12.6, 6.9Hz, 2H), 2.92 (t, J = 7.1 Hz, 2H). ESI MS: 443 (M+1).

Example 144: Compound 144



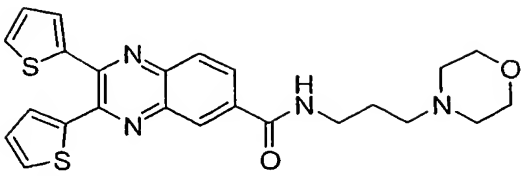
2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(4-pyridyl)ethyl] amide. Purified by preparatory TLC using 10% methanol in dichloromethane as eluant (28 mg, 92%): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.13 (t, J = 6.0 Hz, 1H), 8.65 (d, J = 1.8Hz, 1H) 8.62 (d, J = 6.0 Hz, 2H), 8.33 (dd, J = 8.7, 1.8 Hz, 1H), 8.24 (d, J = 8.7 Hz, 1H), 7.99 (m, 2H), 7.40 – 7.47 (m, 4H), 7.28 (t, J = 4.2 Hz, 2H), 3.77 (dd, J = 12.9, 7.2 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H). ESI MS: 443 (M+1).

Example 145: Compound 145



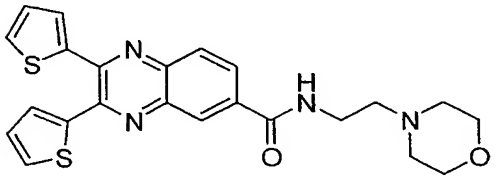
2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid 3-(phenyl)propyl amide. Purified by preparatory TLC using 10% ethyl acetate in dichloromethane as eluant (36 mg, 100%): ESI MS: 456 (M+1).

Example 146: Compound 146



2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [3-(morpholin-4-yl)propyl] amide. Purified by preparatory TLC using 10% methanol in dichloromethane as the mobile phase (33 mg, 100%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.99 (t, J = 5.4 Hz, 1H), 8.63 (d, J = 1.8Hz, 1H), 8.31 (dd, J = 8.7, 1.8 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.93 (dt, J = 6.0, 1.2 Hz, 2H), 7.37 (ddd, J = 10.5, 3.6, 1.2 Hz, 2H), 7.24 – 7.20 (m, 2H), 3.68 (t, J = 4.5 Hz, 4H), 3.42 (m, 2H), 2.46 (m, 6H), 1.83 (m, 2H). ESI MS: 465 (M+1).

Example 147: Compound 147



2,3-Di-thiophen-2-yl-quinoxaline-6-carboxylic acid [2-(morpholin-4-yl)ethyl] amide. Purified by preparatory TLC using 10% methanol in dichloromethane as the mobile phase (29 mg, 93%): ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.66 (t, J = 5.4 Hz, 1H), 8.35 (d, J = 1.8Hz, 1H), 8.02 (dd, J = 8.7, 1.8 Hz, 1H), 7.9 (d, J = 8.7 Hz, 1H), 7.93 (dt, J = 5.7, 1.2 Hz, 2H), 7.08 (ddd, J = 10.5, 3.6, 1.2 Hz, 2H), 6.92 – 6.95 (m, 2H), 3.39 (m, 4H), 3.26 (dd, J = 12.6, 6.3 Hz, 2H), 2.25 – 2.31 (m, 6H). ESI MS: 451 (M+1).

Biological Assays

The materials used for the biological assays are listed below. The materials for the assays were included Streptavidin-coated 96-well plate (Pierce #15502B); substrate peptide Biotin-(Ahx)-GGPKGPGRRGRRRTSSFAEG-COOH based on the PKB target motif of GSKβ; xoluble form of human PKB1 was mutated at threonine 308 to aspartic acid and expressed as a GST fusion protein in insect cells (GST-PKB T308D); 96-well plate for luminescent applications (ThermoLabsystems, #7572); mouse anti-GSK-3β (capture antibody) (BD Transduction Labs #610202); rabbit anti-phospho-GSK-3α/β (detection antibody) (Cell Signaling Technology #9331); anti-rabbit IgG-HRP (Pierce #31460); recombinant Human IGF-1 (R&D Systems #291-G1); and superSignal ELISA Pico Chemiluminescent Substrate (Pierce, #37070).

Example 148: *In Vitro* PKB activity assay

50 µl/well of 5 µg/ml substrate peptide was added to the streptavidin plates overnight at 4°C at in PBS with 100 µg/ml ovalbumin. The plates were washed 3x 300 ul with PBS and 38 µl of kinase buffer (25 mM Tris pH 7.5, 2 mM DTT, 10 mM $MgCl_2$) containing 50 ng GST-PKB T308D was added to each well. Test compounds were diluted in 100% DMSO to 25x final concentration and 2 µl was added to each well. The kinase reaction was started by the addition of 10 µl mixture of 10 µM ATP and 75 nCi/ul ^{33}P-ATP and incubated at room temperature for 45 minutes. The reaction was stopped by adding 50 µl/well of 125 mM EDTA and the plates were washed 5x in 300 µl of PBS containing 0.05% Tween-20. 100 µl of scintillant were added to each well and the incorporated ^{33}P-ATP was measured by scintillation counting. See the tables above for the results of the *in vitro* activity assay.

Example 149: Cell-Based Assay

MCF-7 cells were seeded at 500,000 /well in 6-well plates and serum starved for 48 hours prior to the assay. The test compounds were added to the cells for two hours prior to the initiation of the assay. The cells were treated for 30 min. in the presence or absence of 10 nM IGF-1 and lysed with 100-150 ul lysis buffer (20mM Tris-HCl, pH 7.4, 137 mM NaCl, 1% Triton X-100, 2mM EDTA, 10% glycerol, 0.1 mM Na3VO4) on ice. The lysates were cleared by centrifugation and 50 µl of each lysate was added to 96-well plates coated overnight with 50 µl per well of 4 µg/ml capture antibody. The lysates were incubate at RT for 5 hr and washed 3 x in wash buffer (25 mM Tris, pH 7.5, 0.15 M NaCl and 0.1% Tween-20). The detection antibody was diluted to 1 µg/ml and 50 µl were added to each well at 4°C overnight. The plates were washed 3 x in wash buffer and incubated for 2 hr at RT with 50 µl of anti-rabbit IgG-HRP diluted to 200 ng/ml. The plates were washed 3 x in wash buffer and developed with 100 µl chemiluminescent substrate per well. The plates were read in a TR717 Microplate luminometer (Applied Biosystems) for 1 second. The response (R) was defined as the luminescence units (LU) obtained with IGF-1-treated cells minus (LU) obtained with untreated cells. % inhibition of a compound was calculated as: $\%I = [1-(R_{sample}/Rcontrol)]x\ 100$.